CLINICAL STUDY PROTOCOL

Protocol Number: BT-11-201; Phase 2

US IND Number: 138071

EudraCT Number: 2018-005086-39

A Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Evaluate Efficacy and Safety of Oral BT-11 in Mild to Moderate Ulcerative Colitis

Protocol Amendment 03
03 November 2020

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PROTOCOL APPROVAL PAGE

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Signing Time: 11/3/2020 | 7:51:36 PM PST
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Dr. Josep Bassaganya-Riera
Study Director, Landos Biopharma Inc.

Date

PROTOCOL AMENDMENT 03 SUMMARY OF CHANGES

This document describes the changes in the protocol incorporating Amendment 03. The following is a summary of the changes made in the amendment:

1. In Sections 2.1.1, 8.2.8, 8.3.1.1, 12.3.1 and the synopsis, the primary endpoint definition of clinical remission was changed to the 3-component modified Mayo score, defined as a rectal bleeding subscore of 0, a stool frequency subscore of 0 or 1, and an endoscopic subscore of 0 or 1. Reference 15 was added to the Reference List.

   Justification: The primary endpoint definition was changed based on the current FDA recommendation for a pivotal study endpoint as outlined in the FDA Guidance titled "Ulcerative Colitis: Clinical Trial Endpoints, Guidance for Industry" issued in August 2016.

2. In Sections 2.1.1 to 2.1.3, Section 2.2.1, and Section 12.2 (new), details of estimands for key efficacy endpoints were added.

   Justification: To address the statistical requirements outlined in the International Council for Harmonisation (ICH) E9(R1) "Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials" guidance (20 November 2019).

3. In Sections 3, 5.2 and 12.5 and the synopsis, the Week 12 analysis was adjusted to be a data lock and final analysis of the induction primary endpoint, key secondary endpoints, and Week 12 adverse event data.

   Justification: The data sets pertaining to these endpoints for the full induction cohort will be locked to enable final analysis of data from the study.

4. In Section 2.1.2, Section 8.3.1.2.1, Section 12.3.2, and the synopsis, the order of the key ranked secondary endpoints was changed.

   Justification: The order of the key ranked secondary endpoints were updated to focus the final analysis of primary and key ranked secondary induction efficacy endpoints on the outcomes related to the Mayo score and its components.

5. In Sections 2.1.2 and 8.3.1.2.2, other secondary endpoints were added for mean change in the 3-component modified Mayo Score (Week 12) and Mayo Clinic Score (MCS) clinical remission based on alternate definition of Mayo Score ≤ 2 with all subscores ≤ 1.

   Justification: Changes to the definition of other secondary and exploratory analyses to be in accordance with the primary endpoint definition in this amendment and addition of the previous primary endpoint as a secondary endpoint.

6. In Sections 2.1.3 and 8.3.1.3.1, added exploratory endpoints for mean change in 3-component modified Mayo Score (Week 30) and durable clinical remission based on alternate MCS clinical remission definition.

   Justification: New exploratory endpoints based on 3-component Mayo Score defined in this amendment and defining durable clinical remission using both new definition and previous primary endpoint definition ("MCS clinical remission")

7. In Section 12.1.2, Section 12.3, and the synopsis, the primary analysis population, used for the efficacy analyses, was changed from the intent-to-treat (ITT) population to the modified intent-to-treat (mITT) population, defined as "all randomized subjects who had at least 1 dose of study drug."

   Justification: The naming of the population was changed to align more correctly with the population definition of "all randomized subjects who had at least 1 dose of study drug."

8. In Section 12.3 and the synopsis, clarified that the robustness analysis using the per-protocol analysis set would be performed for the primary and key secondary efficacy endpoints.

   Justification: To clarify that the original intent of the robustness analysis using the per-protocol analysis set was to verify the impact on primary and key secondary endpoints only.

9. In Section 12.3.1, Section 12.3.2, and Appendix 1, statistical analysis details were added to align with the statistical analysis plan.

   a. Added explanation of the order of testing of the secondary key ranked endpoints.

   b. Added details of repeated measures analysis methods in Section 12.3.2.

   c. Clarified that convention based on average of 3-day period for stool frequency and rectal bleeding scoring in Appendix 1 applies to efficacy analyses.

   Justification: To align with the planned statistical analyses.

10. The Section 12.5 title was changed from "Interim Analyses" to "Data Locks."

    Justification: To clarify that these planned analyses involve the final data lock and final analyses for particular data sets and timepoints.

11. In Section 12.6, a justification was added for the parameters used in the sample size calculation and Reference 20 (Sandborn 2016) was added to the Reference List.

Justification: The reference for the original sample size calculation, and the justification for the sample size (given the change in primary endpoint) was added for clarity.

12. Section 12.8, Sensitivity Analysis, was added to describe the planned sensitivity analyses of the primary and secondary endpoints.

    Justification: *To address the statistical requirements outlined in the International Council for Harmonisation (ICH) E9(R1) "Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials" guidance (20 November 2019).*

13. For the induction period of the study (Time and Events Schedule), the Visit 5 procedure window was extended from a ±7-day window to a ±14-day window.

    Justification: To allow greater flexibility for the subjects to complete Visit 5 given the COVID-19 pandemic and the impacts on scheduling procedures near the holiday period.

14. In the Time and Events Schedule for the open-label extension (OLE) period, collection of concomitant medication information and adverse event assessment were added at Visit 3. Return visit scheduling was added at Visit 3 and at the end of treatment (EOT) visit. The requirement to dispense study drug using interactive web-based response system (IWRS) at the EOT visit was removed

    Justification: To correct minor errors in the Time and Events Schedule.

15. Throughout the protocol, "Robarts Clinical Trials, Inc." was updated to "Alimentiv, Inc. (Alimentiv)" to reflect the organization's current name.

16. Minor changes related to consistency, correction of typographical errors, or formatting.

INVESTIGATOR AGREEMENT

A Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Evaluate Efficacy and Safety of Oral BT-11 in Mild to Moderate Ulcerative Colitis

I have read the protocol and agree that it contains all necessary details for carrying out this trial. I undertake to conduct this trial within the time designated.

I understand that all information concerning the study drug supplied to me by the sponsor in connection with this trial and not previously published is considered confidential information.

The information includes the clinical protocol, the case report form, technical methodology, and basic scientific data provided in the Investigator Brochure. I agree that documents and other data pertinent to this trial are the property of the sponsor.

Furthermore, I understand that any changes in the protocol must be approved in writing by the sponsor.

By my signature below, I hereby attest that I have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in the above protocol.

Investigator:

Name and Title	Signature	Date

Name, Address, and Telephone Number of Investigational Site:

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PROTOCOL SYNOPSIS

Title

A Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Evaluate Efficacy and Safety of Oral BT-11 in Mild to Moderate Ulcerative Colitis

Objectives

The primary objective of this study is to establish the efficacy of oral BT-11 in inducing clinical remission at Week 12 in subjects with mild to moderate ulcerative colitis (UC).

The secondary objectives of this study are to evaluate the following at Week 12:

1. The effects of BT-11 on disease activity measured by symptoms, endoscopy, histology, and biomarkers
2. Health-related quality of life
3. The pharmacokinetic (PK) parameters of BT-11
4. Safety

The exploratory objectives of this study are to evaluate the following through Week 30:

1. The effects of BT-11 on disease activity measured by symptoms, endoscopy, histology, and biomarkers
2. Health-related quality of life
3. The PK parameters of BT-11
4. Safety
5. Target engagement and mechanism of action
6. The association of drug exposure in colonic mucosal tissue biopsies with clinical, endoscopic, histopathologic, cellular, and molecular outcomes

Study Design

This is a phase 2 randomized, placebo-controlled, double-blind, parallel-group multicenter study with an optional open-label extension (OLE) period. The purpose of this study is to evaluate the efficacy and safety of oral BT-11 compared to placebo in subjects with mild to moderate UC.

This study includes 3 periods: induction, maintenance, and an optional OLE period.

Induction Period:

Following a 28-day screening period, a total of 195 subjects with mild to moderate UC (total Mayo Score 4-10; Mayo endoscopic subscore [MES] ≥ 2) are planned to be enrolled into this study from approximately 46 sites in Europe and the United States. Eligible subjects will be randomized in a 1:1:1 ratio to receive BT-11 low-dose (500 mg), BT-11 high-dose (1,000 mg) or placebo. Each of the treatment arms will comprise 65 subjects. The randomization will be stratified by prior exposure to biologic therapy for UC (yes/no; exposed population limited to 30% of total sample) and corticosteroid use at baseline (yes/no).

A data lock and final induction phase analysis of the Week 12 primary endpoint, Week 12 key ranked secondary endpoints, and Week 12 AE listings will be conducted after all subjects have reached Week 12. At the Week 12 Visit, subjects who are responders (clinical response and/or clinical remission) and meet all other maintenance continuation requirements may continue blinded study drug until central endoscopy results are available (within approximately 1 week of the endoscopy) for confirmation of eligibility for the maintenance period. Subjects who are nonresponders at Week 12, or who lose response during the maintenance period, or who complete the Week 30 study will be eligible for the optional OLE period.

Maintenance Period:

All subjects who complete the induction period and are responders at Week 12 will enter the 18-week maintenance period. Subjects who continue to the maintenance period will receive the same blinded study drug as the induction period until Week 30. If a subject loses response during the maintenance period, they may have the option to move into the OLE after completing the early termination visit.

OLE Period:

Subjects who a) completed the induction period and were nonresponders at Week 12, or b) lost response during the maintenance period, or c) completed the blinded maintenance period (through Week 30) of that study will have the option to enter the OLE period. Eligible subjects will start open label treatment within approximately 2 weeks after their last dose of study drug in the induction or maintenance period. Subjects who are classified as nonresponders after 12 weeks of therapy in the OLE will be discontinued from the study. Subjects who continue to respond to study treatment will have the option of remaining on BT-11 until the therapy becomes commercially available, or until the sponsor decides to terminate the study or offers an alternate OLE study.

Study Population

The study will include 195 subjects with mild to moderately active UC. Subjects with prior exposure to biologic therapy will be limited to 30% of the total sample. After 58 subjects with prior exposure to biologic therapy have been randomized into the induction period, recruitment will be limited to biologic-naïve subjects.

Key inclusion criteria: male and female subjects aged 18 to 75 years with a diagnosis of UC for at least 3 months; mild to moderate UC defined by a total Mayo Score of 4 to 10 with MES $\geq$ 2 (confirmed by central reader); prior biologic must have stopped at least 8 weeks before study and previous biologic treatment failure is limited to 1 class of biologic; 5-aminosalicylates (max 4.8 g/day) and oral corticosteroids (max 20 mg/day prednisone or equivalent) must be stable for the 12-week induction period.

Key exclusion criteria: severe UC defined by modified Truelove and Witts criteria; disease activity limited to distal 15 cm (proctitis); treatment with immunosuppressant within 25 days prior to randomization; current bacterial or parasitic pathogenic enteric infection; live virus vaccination within 1 month prior to screening.

Maintenance Continuation Criteria:

Key maintenance continuation criteria: meeting eligibility requirements for clinical response and/or clinical remission at Week 12, centrally read confirmation of response is received within 2 weeks of completing the Week 12 visit, and agreeing to a corticosteroid tapering regimen starting at Week 12 with maintenance of stable doses of any other nonprohibited concomitant medications for UC during the rest of the study.

OLE Continuation Criteria:

Key OLE inclusion criteria: All subjects who a) completed the induction period of that study and were nonresponders at Week 12 of the induction period, or b) lost response during the maintenance period, or c) completed the blinded maintenance period (through Week 30). Eligible subjects will start open label treatment within approximately 2 weeks after their last dose of study drug in the induction or maintenance period.

Key OLE exclusion criteria: Experiencing a serious adverse event (SAE) that was considered related to study drug during participation in the induction or maintenance period; pregnancy or lactation in females; diagnosis, medication, or change in circumstance since enrollment in the induction or maintenance period that meets certain exclusion criteria from that period.

Treatments, Dosage, and Administration

Subjects will be randomized to receive BT-11 low-dose (500 mg), BT-11 high-dose (1,000 mg), or placebo once daily for 12 weeks during the induction period of the study. Subjects who continue to the maintenance period will remain in the same blinded treatment group to which they were originally randomized. Authorized personnel at the investigative site will administer the first dose of the study drug or placebo in a blinded fashion. All tablets administered (placebo and BT-11) will have the same appearance and size. Each subject will receive blister packs of the study drug (high-dose BT-11, low-dose BT-11, or placebo).

In the OLE, all subjects will receive BT-11 high-dose (1,000 mg) and study treatment will not be blinded.

Efficacy Evaluations

Induction and Maintenance:

Primary Efficacy Endpoint:

- Clinical remission rate at Week 12, defined using the 3-component modified Mayo Score as a rectal bleeding subscore of 0, a stool frequency subscore of 0 or 1, and an endoscopic subscore of 0 or 1

Key Secondary Endpoints (ranked):

- Endoscopic remission rate at Week 12, defined as an MES of 0 or 1
- Endoscopic response rate at Week 12, defined as a decrease from baseline in MES of ≥ 1 point
- Clinical response rate at Week 12, defined as decrease from baseline in Mayo Score of ≥ 3 points and ≥ 30%, with an accompanying decrease in the subscore for rectal bleeding of ≥ 1 point or an absolute subscore for rectal bleeding of 0 or 1
- Mucosal healing rate at Week 12, defined by a MES of 0 or 1 and a Geboes score < 3.1
- Histologic remission rate at Week 12, defined by a Geboes score < 3.1

Other Secondary Endpoints:

- Mean change in 3-component modified Mayo score from baseline to Week 12
- Mean change in partial Mayo Score from baseline to Weeks 2, 6, and 12
- Mean change in Mayo rectal bleeding subscore from baseline to Weeks 2, 6, and 12
- Mean change in Mayo stool frequency subscore from baseline to Weeks 2, 6, and 12
- Mean change in MES from baseline to Week 12
- Mean change in Robarts Histopathology Index (RHI) scores from baseline to Week 12
- Mean change in fecal calprotectin from baseline to Weeks 2, 6, and 12
- Clinical remission rate at Week 12, based on alternate definition ("Mayo Clinic Score [MCS] clinical remission") of total Mayo Score ≤ 2 with all subscores ≤ 1
- Normalization of fecal calprotectin from baseline to Weeks 2, 6, and 12 in subjects with abnormal fecal calprotectin at baseline (abnormal defined as fecal calprotectin > 250 mg/kg)
- Normalization of hs-CRP at Weeks 2, 6, and 12 in subjects with abnormal hs-CRP at baseline (abnormal defined as hs-CRP > 3.0 mg/L)
- Mean change in high-sensitivity C-reactive protein (hs-CRP) from baseline to Weeks 2, 6, and 12
- Mean change in UC-100 score from baseline to Week 12

- Change in Robarts Symptom and Impacts Questionnaire for Ulcerative Colitis (SIQ-UC) items from baseline to Week 12
- Mean change in Inflammatory Bowel Disease Questionnaire (IBDQ) score from baseline to Week 12
- BT-11 concentration in serum, feces, and tissue

Exploratory Endpoints:

- Durable clinical remission, defined as clinical remission at both Week 12 and Week 30
- Durable clinical remission (defined as MCS clinical remission at both Week 12 and Week 30)
- Durable clinical response, defined as clinical response at both Week 12 and Week 30
- Endoscopic remission rate at Week 30, defined as an MES of 0 or 1
- Endoscopic response rate at Week 30, defined as a decrease from baseline in MES of ≥ 1 point
- Corticosteroid-free clinical remission at Week 30
- Corticosteroid-free endoscopic remission at Week 30
- Mucosal healing rate at Week 30 as defined by a MES of 0 or 1 and a Geboes score < 3.1
- Histologic remission rate at Week 30 as defined by a Geboes score < 3.1
- Clinical response rate at Week 30, defined as decrease from baseline in Mayo Score of ≥ 3 points and ≥ 30%, with an accompanying decrease in the subscore for rectal bleeding of ≥ 1 point or an absolute subscore for rectal bleeding of 0 or 1
- Mean change in 3-component modified Mayo score from baseline to Week 30.
- Mean change in partial Mayo Score from baseline to Weeks 18, 24, and 30
- Mean change in Mayo rectal bleeding subscore from baseline to Weeks 18, 24, and 30
- Mean change in Mayo stool frequency subscore from baseline to Weeks 18, 24, and 30
- Mean change in MES from baseline to Week 30
- Mean change in RHI scores from baseline to Week 30
- Mean change in fecal calprotectin from baseline to Weeks 18, 24, and 30
- Normalization of fecal calprotectin at Weeks 18, 24, and 30 in subjects with abnormal fecal calprotectin at baseline (abnormal defined as 250 mg/kg)
- Normalization of hs-CRP at Weeks 18, 24, and 30 in subjects with abnormal hs-CRP at baseline (abnormal defined as hs-CRP > 3.0 mg/L)
- Mean change in hs-CRP from baseline to Weeks 18, 24, and 30
- Mean change in UC-100 score from baseline to Week 30
- Change in Robarts SIQ-UC items from baseline to Week 30
- Mean change in IBDQ score from baseline to Week 30
- BT-11 concentration in serum, feces, and tissue at Week 30 in the active BT-11 treatment groups

Other Exploratory Endpoints

- Immunohistochemistry on formalin-fixed, paraffin-embedded colonic mucosal tissue biopsies

- Multiplex cytokine analysis in serum and tissue
- Transcriptomic analysis on colonic mucosal tissue biopsies using quantitative polymerase chain reaction (qPCR)
- Flow cytometry on colonic mucosal tissue biopsies
- Exposure-response analysis

Safety Evaluations

- Frequency and severity of adverse events (AEs) compared to placebo
- Changes in clinical chemistry and hematology from baseline
- Results of vital signs and physical examination
- Electrocardiogram (ECG) findings

Open-Label Extension

Safety Endpoints

- Percentage of subjects with treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs that lead to discontinuation of study drug at each study visit.
- Results of vital signs and physical examination

Exploratory Efficacy Endpoints

- Partial Mayo Score clinical remission, defined as a partial Mayo Score < 2, at each study visit
- Partial Mayo Score clinical response, defined as a decrease in the partial Mayo Score of ≥ 2 points from Day 1, at each study visit
- Mean change in partial Mayo Score from Day 1 to each study visit
- Mean change in Mayo rectal bleeding subscore from Day 1 to each study visit
- Mean change in Mayo stool frequency subscore from Day 1 to each study visit

Statistical Methods

A sample size of 65 randomized subjects to each of 3 treatment groups during the induction period is expected to provide evaluable data on approximately 63 subjects per group at Week 12. This sample size will allow for the detection of a 17-percentage point change in remission rate (assuming a 5% placebo endoscopic remission rate) between groups, with a type I error rate of < 0.05 and 80% power.

Efficacy analyses will primarily be based on the modified intent-to-treat (mITT) analysis set. A robustness analysis of the primary and key secondary efficacy endpoints will also be performed on the per-protocol (PP) analysis set. Statistical tests will be 2-sided and performed at the 0.05 level of significance.

The proportion of subjects with clinical remission at Week 12 (defined using the 3-component modified Mayo Score as a rectal bleeding subscore of 0, a stool frequency subscore of 0 or 1, and an endoscopic subscore of 0 or 1) for each group will be tested with a Cochran-Mantel-Haenszel test, stratified with respect to previous use of biologic therapy (yes/no; exposed population limited to 30% of total sample) and oral corticosteroid use at baseline (yes/no).

A closed hierarchical procedure will be used to control for multiple comparisons. The order of testing will begin with high dose versus placebo at Week 12. If this result is significant at the 2-sided P < .05 then the

low-dose versus placebo at Week 12 will be tested, followed by subsequent ranked key secondary analyses. In this regard, the first ranked secondary endpoint will be tested first for the high dose, and subsequently for the low dose provided $P < .05$ for the high dose. Testing will continue in a similar manner for the subsequent ranked secondary endpoints with high dose tested prior to low dose. If at any point in this sequential procedure the $P < .05$ is not met, the testing procedure will be terminated. All subsequent analyses would be considered exploratory.

A data lock and final induction phase data analysis of the Week 12 primary endpoint, Week 12 key ranked secondary endpoints, and Week 12 AE listings will be performed when all subjects have completed the induction period (or discontinued study treatment). To minimize any bias being introduced into the analysis, all data during the assessment period associated with the primary endpoint, key ranked secondary endpoints, or AE listings as of Week 12 must have been monitored, the induction period statistical analysis plan (SAP) must be finalized and approved, and definitions of analysis populations must be finalized (including classification of significant protocol deviations and decision regarding exclusion of any subjects from the induction study analysis) before the partial database lock and before unblinding.

As this will be the final analysis of the primary and key ranked secondary endpoints, no adjustment of type I error will be performed. The induction analysis will be conducted by a limited number of preidentified team members who do not have direct site contact or data entry/validation responsibilities. Unblinding details will be specified in the unblinding plan section of the SAP or in a separate unblinding plan document. Information that may unblind the study during the final analyses of induction data will not be reported to study sites or the blinded study team until the study has been unblinded.

A second analysis (maintenance data lock and analysis) will be performed to assess the remaining Week 12 secondary and exploratory endpoints and the Week 30 efficacy and safety results after all subjects have completed the maintenance period (or discontinued study treatment). No type 1 error adjustment will be necessary for the analyses of the additional non-ranked secondary endpoints and exploratory endpoints. This will be the final analysis for many of the secondary and exploratory efficacy endpoints out to Week 30. Once the maintenance data lock is complete, the study will be unblinded.

Before each data lock, the applicable SAP must be finalized as well as coding of events, medications and assessment of any major protocol deviations.

The final database lock and analysis of the OLE period data will be carried out when the study ends.

TIME AND EVENTS SCHEDULE – INDUCTION PERIOD

Study Procedure	**Screening**	**Randomization**	**Induction**			**Safety Follow-up**	**Unscheduled**
Visit	**1** [a]	**2** [b]	**3**	**4**	**5** [c, d]	**(W2PT)** [e]	**UNS** [d, f]
Week	**S**	**R**	**2**	**6**	**12/EOT/ Assess** [g]	**W2PT**	
Study day	**-28 to 0**	**1**	**15 ±3**	**43 ±7**	**85 ±14**	**(W2PT ±7)**	
Informed Consent [h]	X						
Assess Inclusion/Exclusion	X				(X) [g]		
Confirm Inclusion/Exclusion		X					
Randomization		X					
Demographics	X						
Medical/Surgical History, Medication History	X						
Physical Exam	X	X	X	X	X	(X)	
Vital Signs [i], Weight	X	X	X	X	X	(X)	
BMI	X				X		
Hematology	X		X	X	X	(X)	
Serum Chemistry	X		X	X	X	(X)	
Urinalysis	X		X	X	X	(X)	
Serum Pregnancy Test [j]	X				X		
Urine Pregnancy Test [j]		X	X	X			
Serum for hs-CRP	X		X	X	X		
Serum for Multiplex Cytokine Analysis		X	X	X	X		
Fecal Sample for *C. diff.*	X						
Fecal Calprotectin	X		X	X	X	(X)	
12-lead ECG	X				X		
IBDQ		X			X		
Blood Sample for PK [k]		X	X	X	X		
Stool Sample for PK		X	X	X	X		
Endoscopy with Biopsy (11 samples)	X [l]				X		
Full Mayo Score	X				X		
Partial Mayo Score		X	X	X			
Centrally Read MES	X				X		
Centrally Read Geboes Score (with RHI calculation)	X				X		
UC-100	X				X		
Robarts SIQ-UC (if available)	X	X	X	X	X		
Review Subject Diary Instructions	X						

Study Procedure	**Screening**	**Randomization**	**Induction**			**Safety Follow-up**	**Unscheduled**
Visit	**1** [a]	**2** [b]	**3**	**4**	**5** [c, d]	**(W2PT)** [e]	**UNS** [d, f]
Week	**S**	**R**	**2**	**6**	**12/EOT/ Assess** [g]	**W2PT**	
Study day	**-28 to 0**	**1**	**15 ±3**	**43 ±7**	**85 ±14**	**(W2PT ±7)**	
Subject Diary (daily rectal bleeding and stool frequency)	X	X	X	X	X		
Review Subject Diary Compliance		X	X	X	X		
IWRS Randomization		X					
Dispense Study Drug		X	X	X	(X) [m]		
Study Drug Accountability			X	X	X		
Concomitant Medications	X	X	X	X	X	(X)	X
Adverse Event Assessment	X [n]	X	X	X	X	(X)	X
Schedule Return Visit	X	X	X	X	X [o]		

Abbreviations: BMI, body mass index; *C. diff.*, *Clostridium difficile*; D, day; ECG, electrocardiogram; EOT, end of treatment; hs-CRP, high-sensitivity C-reactive protein; IBD, inflammatory bowel disease; IBDQ, Inflammatory Bowel Disease Questionnaire; IWRS, interactive web-based response system; MES, Mayo endoscopic subscore; PK, pharmacokinetic; PT, posttreatment; R, randomization; RHI, Robarts Histopathology Index; S, screening; SIQ-UC, Symptoms and Impact Questionnaire for Ulcerative Colitis; UNS, unscheduled; W2PT = week 2 posttreatment.

a Once informed consent is obtained, listed procedures may be performed at any time during the screening period.

b Randomization may occur at any point within 28-day window when all screening procedures have been completed and all results required to assess eligibility are available.

c If subject withdraws from the induction period early, perform Visit 5 procedures.

d If a subject returns for an unscheduled visit and it is determined that the subject should be withdrawn from the study during the induction period and prior to Week 12, perform Visit 5 procedures.

e For subjects who are exiting the study at Week 12, perform posttreatment (W2PT) procedures 14 days ± 7 days after the last study drug dose. Subjects who are continuing to the maintenance period will not have a safety follow-up until they exit the study. Subjects who are continuing to the open-label extension (OLE) period will not be required to complete this W2PT visit.

f The results of any study-related procedures performed at an unscheduled visit will be recorded and collected for the study, such as clinical laboratory tests or retests.

g Subjects who complete the study to Week 12 and are classified as responders may move into the maintenance period of the study following assessment of the maintenance continuation criteria (see the Time and Events Schedule – Maintenance Period).

h The informed consent process can begin prior to Visit 1, for example, if washout from medications is required.

i At all visits, includes blood pressure, heart rate, respiratory rate, temperature, and orthostatic vital signs.

j Only required for women of childbearing potential.

k To be collected as a single sample at time of the visit with note made of timing postdose (time of previous dose and time of PK sample will be collected).

l The endoscopy procedure should be scheduled at least 5 days prior to the planned randomization visit to allow for central reading.

m Subjects who appear to be responders (clinical response and/or clinical remission) at the Week 12 visit, pending central endoscopy results, and meet all other maintenance continuation requirements may continue on blinded study drug until central endoscopy results are available (within approximately 1 week of the endoscopy) for

confirmation of eligibility. If a subject subsequently fails to meet endoscopic criteria for responders, a final follow-up visit must be performed 2 weeks after date of last dose of study drug.

n Record adverse events from the time of the signing of the informed consent.

o Subjects who appear to be responders at the Week 12 visit will be contacted to confirm the next visit as either Week 13 (continuation to maintenance) or 2-week Safety Follow-up once central reading results are obtained.

TIME AND EVENTS SCHEDULE – MAINTENANCE PERIOD

Study Procedure		**Maintenance Follow-up**			**Safety Follow-up**	**Unscheduled**
Visit [a]	**6**	**7**	**8**	**9/EOT** [b, d]	**10** [c]	**UNS** [d, e]
Week [a]	**13**	**18**	**24**	**30**	**W2PT**	
Study Day [a]	**92 ±7** [f]	**127 ±14**	**169 ±7**	**211 ±7**	**(W2PT ±7)**	
Confirm Continuation Criteria (central reading has confirmed response)	X					
Physical Exam		X	X	X	X	
Vital Signs [g], Weight		X	X	X	X	
BMI				X		
Hematology		X	X	X	X	
Serum Chemistry		X	X	X	X	
Urinalysis		X	X	X	X	
Serum Pregnancy Test [h]				X		
Urine Pregnancy Test [h]		X	X			
Serum for hs-CRP		X	X	X		
Serum for Multiplex Cytokine Analysis		X	X	X		
Fecal Calprotectin		X	X	X	X	
12-lead ECG				X		
IBDQ				X		
Blood Sample for PK [i]		X	X	X		
Stool Sample for PK		X	X	X		
Endoscopy with Biopsy (11 samples)				X		
Full Mayo Score				X		
Partial Mayo Score		X	X			
Centrally Read MES				X		
Centrally Read Geboes Score (with RHI calculation)				X		
UC-100				X		
Robarts SIQ-UC (if available)		X	X	X		
Review Subject Diary Instructions	(X) [j]					
Subject Diary (rectal bleeding and stool frequency)	X [k]	X [k]	X [k]	X [k]		
Review Subject Diary Compliance	X	X	X	X		
Dispense Study Drug	X	X	X			
Study Drug Accountability	X	X	X	X		
Concomitant Medications	X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X
Relapse Assessment [l]		X	X			
Schedule Return Visit	X	X	X	X		

Abbreviations: BMI, body mass index; D, day; ECG, electrocardiogram; EOT, end of treatment; hs-CRP, high-sensitivity C-reactive protein; IBD, inflammatory bowel disease; IBDQ, Inflammatory Bowel Disease Questionnaire; MES, Mayo endoscopic subscore; PK, pharmacokinetic; PT, posttreatment; RHI, Robarts Histopathology Index; SIQ-UC, Symptoms and Impact Questionnaire for Ulcerative Colitis; UNS, unscheduled; W2PT = week 2 posttreatment.

a The maintenance period of the study will begin at Week 13, once central endoscopy results are available and continuation criteria have been confirmed.

b If subject withdraws from the maintenance period early, perform Visit 9/EOT procedures.

c Perform posttreatment (Visit 10) procedures 14 days ± 7 days after the last study drug dose. Subjects who are continuing to the open-label extension (OLE) period will not be required to complete this W2PT visit.

d If a subject returns for an unscheduled visit and it is determined that the subject should be withdrawn from the maintenance period, perform Visit 9/EOT procedures.

e The results of any study-related procedures performed at an unscheduled visit will be recorded and collected for the study, such as clinical laboratory tests or retests.

f The Week 13 visit will take place once central reading scores are available and continuation criteria can be confirmed (within approximately 2 weeks of completing the Week 12 visit).

g At all visits, includes blood pressure, heart rate, respiratory rate, temperature, and orthostatic vital signs.

h Only required for women of childbearing potential.

i To be collected as a single sample at time of the visit with note made of timing postdose (time of previous dose and time of PK sample will be collected).

j Subjects continuing into the maintenance period of the study will be provided with new instructions for completing the subject diary daily only during the 7 days before each visit.

k During the maintenance period, subjects will be asked to complete the subject diary daily only during the 7 days before each visit.

l At Weeks 18 and 24, if, in the opinion of the investigator, the subject has had a disease relapse, they will be considered a nonresponder and will exit the study (perform Visit 9 procedures) but may have the option to enter the OLE period.

TIME AND EVENTS SCHEDULE – OPEN-LABEL EXTENSION PERIOD

Study Procedure	**Screening**	**Enrollment**	**Treatment**				**Safety Follow-up**	**Unscheduled**
Visit	**1** [a, b]	**2** [c]	**3**	**4**	**Repeat Visits**	**EOT** [d, e]	**W2PT** [e]	**UNS** [f, g]
Week	**S**	**E**	**4**	**12**	**Every 12 Weeks**	**EOT**	**W2PT**	
Study day	**-14 to 0**	**1**	**29 ±7**	**85 ±7**	**169 ±7, etc.**	**Last Dose**	**14 ±7 PT**	
Informed Consent [h]	X							
Assess Inclusion/Exclusion	X							
Confirm Inclusion/Exclusion		X						
Enrollment [i]		X						
Demographics, Medical/Surgical History, Medication History	[j]							
Physical Exam	(X) [b]	X	X	X	X	X	X	
Vital Signs [k], Weight	(X) [b]	X	X	X	X	X	X	
Partial Mayo Score		X	X	X	X	X		
Responder/Loss of Response Assessment				X [l]	X [m]			
Review Subject Diary Instructions	X							
Subject Diary [n] (daily rectal bleeding and stool frequency)		X	X	X	X	X		
Review Subject Diary Compliance		X	X	X	X	X		
Dispense Study Drug Using IWRS		X	X	X	X			
Review Study Drug Compliance			X	X	X	X		
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Assessment	X [o]	X	X	X	X	X	X	X
Schedule Return Visit	X	X	X	X	X	X		

Abbreviations: BMI, body mass index; D, day; E, enrollment; EOT, end of treatment; PT, posttreatment; S, screening; UNS, unscheduled; W2PT = week 2 posttreatment.

a Once informed consent is obtained, listed procedures may be performed at any time during the screening period, if required.

b Subjects coming in from a Week 12 or an EOT visit from the induction or maintenance period that included these procedures within 2 weeks of planned continuation in the open-label extension (OLE) period, do not need to repeat these procedures. These data will be duplicated from the prior study period. Procedures not already performed within 2 weeks prior to planned continuation in the OLE period should be repeated during screening.

c Enrollment may occur at any point within a 14-day window when all screening procedures have been completed and all results required to assess eligibility are available.

d If subject withdraws from the study early, perform EOT visit procedures.

e Perform posttreatment (W2PT) procedures 14 days ± 7 days after the last study drug dose.

f If a subject returns for an unscheduled visit and it is determined the subject should be withdrawn from the study, perform EOT visit procedures.
g The results of any study-related procedures performed at an unscheduled visit will also be recorded and collected for the study, such as clinical laboratory tests or retests.
h The informed consent process can begin prior to Visit 1.
i Eligible subjects will start open label treatment within approximately 2 weeks after their last dose of study drug in the induction or maintenance period.
j Data will be duplicated from the induction and maintenance periods and does not need to be collected again.
k At all visits, includes blood pressure, heart rate, respiratory rate, temperature, and orthostatic vital signs.
l Subjects who are classified as nonresponders at the Week 12 visit, based on the investigator's assessment, will be discontinued from the study. Perform EOT visit procedures.
m Subjects who have loss of response, based on the investigator's assessment, will be discontinued from the study. Perform EOT visit procedures.
n Complete stool diary daily for 1 week leading up to each scheduled visit.
o Record adverse events (AEs) from the time following the last AE assessment of the induction or maintenance period. The same AE should not be reported in the induction/maintenance period and the OLE period. However, any AE that occurred after the prior study period (i.e., was not reported in that study) should be recorded as an AE in this OLE period, even if prior to screening and informed consent.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

5-ASA	5-aminosalicylic acid
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CD	Crohn's disease
CIMS	Central Image Management Solutions
CNS	central nervous system
CRO	contract research organization
CYP450	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
FOXP3	forkhead box P3
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
hERG	human ether-à-go-go-related gene
HRQOL	health-related quality of life
hs-CRP	high-sensitivity CRP
IB	investigator brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Council for Harmonisation
IC_{50}	half maximal inhibitory concentration
IEC	independent ethics committee
IFNγ	interferon-γ
IL	interleukin
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IWRS	interactive web-based response system
LANCL2	lanthionine synthetase C-like 2
LPMC	lamina propria mononuclear cell
MAD	multiple ascending dose
MCP1	monocyte chemoattractant protein-1
MCS	Mayo Clinic Score
MES	Mayo endoscopic subscore
MIP1α	macrophage inflammatory protein-1α
mITT	modified intent-to-treat
MPO	myeloperoxidase
NK	natural killer (cells)
NOAEL	no-observed-adverse-effect level
OLE	open-label extension
PBMC	peripheral blood mononuclear cell
PK	pharmacokinetic
PP	per-protocol
qPCR	quantitative polymerase chain reaction
RHI	Robarts Histopathology Index
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan

TBL	total bilirubin level
TEAE	treatment-emergent adverse events
Th	T helper (cells)
TNFα	tumor necrosis factor-α
Treg	T regulatory (cells)
UC	ulcerative colitis
ULN	upper limit of normal
WOCBP	woman of childbearing potential

1 INTRODUCTION

Inflammatory bowel disease (IBD) is an autoimmune disease of the gastrointestinal (GI) tract with unknown etiology that encompasses 2 primary clinical manifestations: ulcerative colitis (UC) and Crohn's disease (CD). IBD affects over 1.5 million people in North America and 2.5 million in Europe, with a growing global spread and a prevalence of 0.5% of the population in most impacted regions.[1, 2]

UC manifests through complex interactions between the gut microbiome, dysregulated immune responses, genetic mutations, diet, and other environmental factors. As a result, the precise stimulus for the initiation of disease differs widely among patients with UC. Current therapies have limited efficacy and significant side effects. An unmet clinical need remains because CD and UC are not well-managed pharmacologically with current drugs.[3, 4]

Current therapies for UC are modestly successful and have significant adverse side effects including systemic immunosuppression, increased incidence of opportunistic and rare infections and increased risk for cancer.[4] Thus, there remains a significant and unmet clinical need to better manage UC with safer and more effective oral therapies.

Landos Biopharma, Inc. (Landos) has developed a small molecule, oral BT-11, for IBD to target lanthionine synthetase C-like 2 (LANCL2). LANCL2 is a novel therapeutic target for inflammatory and autoimmune diseases.

1.1 BACKGROUND

UC broadly involves defects within both the epithelial barrier and mucosal immune system.[5] In UC, epithelial cells commonly produce lower levels of mucin and form a more permeable barrier layer.[6] These 2 factors result in greater infiltration of and exposure to intestinal bacteria and other microbes. In response, epithelial and immune cells have increased uptake and recognition of antigens, causing a self-perpetuating loop of altered gut microflora, increasing inflammation, and damage to the colonic epithelium.[5] Importantly, many genes involved in antigen uptake and recognition, such as major histocompatibility complexes, toll-like receptors, and Nod-like receptors, are common genetic risk factors for UC.[7, 8]

Immunologically, the balance between inflammatory and anti-inflammatory cell types is skewed in patients with UC. This is most apparent within CD4+ T helper (Th) cells, in which Th1, Th2, and Th17 are elevated at the expense of T regulatory (Treg) cells. Specifically, in UC, Th2 responses are upregulated, increasing production of interleukin 4 and 13 (IL-4 and IL-13), which combine to activate natural killer (NK) T cells.[9] In turn, the NK T cells can attack epithelial cells and weaken tight junctions, compromising the barrier further. The inflammatory environment is further worsened by increased production of tumor necrosis factor alpha (TNFα) and chemokines, such as CXCL8, which activate and recruit additional inflammatory cells to the colon.[5, 10] Interestingly, patients with UC have decreased levels of Treg cells and reduced levels of serum IL-10 while they have increased levels of serum IL-21.[11]

BT-11 is an orally active, gut-restricted, first-in-class small molecule therapeutic with low systemic exposure that binds to and activates LANCL2 which is highly expressed in the immune and epithelial cells of the GI tract. Across 6 preclinical models, BT-11 results in increases of regulatory CD4+ T cells and IL-10 expression, and decreases of neutrophils, Th1 cells, and TNFα, interferon-γ (IFNγ), and monocyte chemoattractant protein-1 (MCP1) expression in the colon. The activation of LANCL2 by BT-11 results in potent immunometabolic effects directly within

immune cells particularly within late-stage glycolysis. These changes manifest in an increase in pyruvate dehydrogenase activity and oxidative phosphorylation that align with the regulatory phenotype in contrast to the lactate-based methods of energy production in activated effector CD4+ T cells. The actions of BT-11, through LANCL2, synergize with IL-2/CD25 signaling to preferentially enhance the phosphorylation of signal transducer and activator of transcription (STAT5) to maintain stable transcription and activation of forkhead box P3 (FOXP3). The net result is an increase in number of Tregs and functionality of Tregs with BT-11 treatment, in which BT-11-treated Tregs have greater ability to suppress proliferation and inflammatory cytokine production and a greater resistance to effector-biased plasticity in inflammatory environments. Established in in vitro and in vivo mouse models, these therapeutic actions have also been observed to translate to primary human cells, peripheral blood mononuclear cells (PBMCs), and colonic lamina propria mononuclear cells (LPMCs) from patients with CD and UC, with similar potency to that observed in murine cells. For the most detailed clinical and nonclinical information, refer to the latest version of the BT-11 Investigator Brochure (IB).

1.2 CLINICAL PHARMACOLOGY AND TOXICOLOGY

BT-11 is a first-in-class orally active drug targeted to the LANCL2 receptor; LANCL2 activation by BT-11 intercepts the pathology of IBD at 2 levels: by decreasing the production of inflammatory mediators (TNFα, IFNγ, IL-4, MCP1) and increasing anti-inflammatory molecules (IL-10, FOXP3) in Treg cells in the GI tract. Preclinical data has shown that BT-11 acts topically targeting the GI tract to reduce inflammation and lesions in 6 different animal models of IBD and compares very favorably with other compounds including systemically administered anti-TNF biologic drugs. The drug appears to be minimally absorbed, and safety studies suggest a favorable safety profile. Good Laboratory Practice (GLP) 180-day rat and 270-day dog repeat-dose toxicity testing has indicated a no-observed-adverse-effect level (NOAEL) of at least 1,000 mg/kg. The results from the genotoxicity and central nervous system (CNS), cardiovascular, and respiratory safety pharmacology studies suggest that the product may be safely administered to humans. Based upon the studies to date, the drug appears metabolically stable, and specific to the LANCL2 receptor. A phase 1 study that combined single ascending doses (SAD) and multiple ascending doses (MAD) was conducted in human volunteers up to doses of 100 mg/kg, approximately 7.5 g of absolute dose. The phase 1 study (N=70) revealed that BT-11 was well tolerated and safe based on standard safety laboratory results with no clinically significant abnormalities; did not increase out-of-range findings in standard biochemistry, hematology, coagulation, or urinalysis laboratory results; and did not significantly change electrocardiogram (ECG) parameters or vital signs. No safety or tolerability issues were identified. Human administration is likely to be constrained at the higher end by volume of drug (maximum achievable dose), but the anticipated therapeutic dose based on preclinical data is well within these limits.

1.2.1 PRIMARY PHARMACOLOGY

BT-11 binds and activates the functions of LANCL2, which increases the production of anti-inflammatory/regulatory markers (IL-10 and FOXP3) while decreasing proinflammatory cytokine production (IFNγ, TNFα, IL-6, IL-8, MCP1). Through metabolic actions on immune cells, related to decreasing the concentration of the glycolysis intermediate phosphoenolpyruvate, BT-11 stabilizes the actions of FOXP3, a critical transcription factor in regulatory CD4+ T cells (Tregs). The therapeutic efficacy of BT-11 in treating IBD has been validated in 5 mouse models of IBD. Due to the multifactorial nature of IBD, a single model of disease is insufficient in demonstrating efficacy. Oral dosing of 8 mg/kg/day BT-11 decreases inflammation, severity of histological

lesions, and overall disease activity in dextran sulfate sodium, IL-10-/-, CD4+ adoptive transfer, MDR1a-/-, and *Citrobacter rodentium* models of IBD. BT-11 has been tested in PBMCs and colonic LPMCs isolated from primary samples from UC donors. Ex vivo BT-11 treatment, in the concentration range of 10 to 100 nM, decreases TNFα, IFNγ, and IL-4 producing cells while increasing IL-10 and FOXP3 expressing cells. Characteristic mechanistic effects in Treg cell differentiation, stability, and function have been observed in PBMCs and LPMCs.

1.2.2 Safety Pharmacology and Toxicology

BT-11 was inactive in 39 out of 44 common adverse drug reaction (ADR) targets at a concentration of 10 µM. BT-11 at 10 µM was observed to have significant inhibition of human Ether-à-go-go-Related Gene (hERG) (95.1% inhibition), dopamine transporter (66.5%), serotonin 5-HT1A (58.6%), 5-HT2B (52.8%) receptors, and norepinephrine transporter (50.6%). Four of the 5 ADRs were tested in a follow-up study at a lower concentration, representing the highest observed individual replicate plasma concentration, 1.2 µM. At this lower concentration, none of these 4 ADRs were significantly inhibited by BT-11. Due to the low systemic exposure, these results suggest a low risk for off-target effects with oral BT-11 dosing. The target with the highest BT-11 inhibition (hERG) was further tested. The activity of BT-11 on hERG-mediated potassium currents displayed a half maximal inhibitory concentration (IC_{50}) of 0.21 µM, a concentration roughly equal to the highest observed average plasma Cmax in dogs dosed orally with 1,000 mg/kg BT-11. Despite this concern no changes in ECG parameters were observed in safety pharmacology studies in dogs up to 1,000 mg/kg.

Oral BT-11 up to a dose level of 1,000 mg/kg displayed no signs of disruption of respiratory, cardiovascular, and CNS organ function. The respiratory, cardiovascular, and neurobehavioral safety of oral BT-11 up to concentrations of 1,000 mg/kg are supported by these studies.

The toxicity of repeated oral dosing of BT-11 was tested in rats up to 180 days and dogs for up to 270 days with a 2-week recovery period (data on file). The NOAEL of BT-11 in rats was 1,000 mg/kg (the highest dose level tested) with no treatment-related adverse events or clinical observations at any of the tested dose levels. No mortality or noteworthy findings were recorded. No differences in food consumption, ophthalmology, gross pathology, hematology, serum chemistry, or histopathology were observed. The NOAEL of BT-11 in dogs was also 1,000 mg/kg (the highest dose level tested). No treatment-related adverse events or clinical observations were observed at any of the dose levels tested. No mortality was recorded in the study. No differences in food consumption, ophthalmology, gross pathology, hematology, serum chemistry, or histopathology were observed at the 1,000 mg/kg dose level. These studies supported a starting dose in the first-in-human clinical study at a nominal 7.7 mg/kg (< 1% of the NOAEL) dose and incrementally escalated to 100 mg/kg (10% of the NOAEL).

The genotoxicity of BT-11 was tested. Tests revealed no genotoxicity concerns with BT-11.

1.2.3 ADME (Absorption, Distribution, Metabolism, and Excretion), Pharmacokinetics, and Toxicokinetics

The metabolic stability of BT-11 was tested in microsomes and hepatocytes from human, rat, and dog origin. In both tests, BT-11 displayed low to moderate clearance in all species tested.

Analysis of BT-11 plasma protein binding in human, dog, and rat demonstrated that the compound is highly protein bound in all 3 species. Plasma BT-11 was protein bound in all 3 species at > 97%.

BT-11 had minimal inhibitory effects on cytochrome P450 (CYP450) enzyme activity with IC_{50} values > 4.56 µM for all CYP450 isoforms. BT-11 did not induce common CYP450 enzymes. The primary metabolizing enzyme of BT-11 was identified to be CYP3A4, with a half-life of 71.6 minutes. No other enzyme was observed to provide a half-life less than 270 minutes. BT-11 did not significantly inhibit the activity of any common GI transporters. BT-11 was observed to inhibit OATP1B1 and OATP1B3 liver transporters with IC_{50} values of 2.6 and 0.39 µM, respectively. However, these concentrations were lower than the active maximum systemic concentrations of BT-11 of approximately 5 nM.

The pharmacokinetics, toxicokinetics, GI, and renal excretion on BT-11 were evaluated in several single- and repeat-dose studies in mice, rats, pigs, and dogs. Systemic exposure was found to be very low in all species following both single and repeat oral dosing up to a dose level of 1,000 mg/kg (the highest dose tested). The highest mean plasma Cmax observed was 210 ng/mL (observed in male dogs dosed with a single dose of BT-11 at 1,000 mg/kg). Furthermore, BT-11 plasma levels in all species tested did not display dose proportionality or accumulation following repeat dosing up to 90 days. In urine, BT-11 concentrations were of the same order of magnitude as plasma suggesting that systemically absorbed BT-11 is excreted in the urine.

GI excretion measurements in mice and pigs demonstrated that BT-11 concentrations in colonic content have dose proportionality and are many orders of magnitude (10,000- to 5,000,000-fold) greater than plasma concentrations suggesting that the majority of oral BT-11 is not systemically absorbed and is excreted in the feces.

1.3 CLINICAL EXPERIENCE

Clinical experience with BT-11 to date comes from a single phase 1 study (N=70 total; 54 BT-11; 16 placebo) to evaluate the safety, tolerability, and pharmacokinetic (PK) profile of BT-11 in healthy volunteers. Subjects were randomized into 5 SAD cohorts (7.7, 25, 50, 75, and 100 mg/kg, orally) and 3 MAD cohorts (7.7, 50, and 100 mg/kg once daily for 7 days, orally).

Safety and tolerability were assessed by adverse event (AE) reporting, vital signs, ECG, hematology, and clinical chemistry. BT-11 did not result in increases in total AE or GI AE rates in individual dose cohorts or in overall pooled active group in SAD or MAD cohorts. No serious adverse events (SAEs) were observed over the course of the study. Oral BT-11 dosing did not result in any clinically significant findings by biochemistry, coagulation, ECG, hematology, or urinalysis when compared to placebo.

Peak plasma concentrations were observed 1 hour after dosing. Plasma concentrations scaled in a less than dose proportional manner with systemic exposure reaching a maximum limit at approximately 75 mg/kg. Plasma half-life was observed to be between 2.7 and 3.2 h. BT-11 did not accumulate systemically after 7 days of once-daily dosing with no changes in PK parameters and 24-hour trough concentrations near or below the lower limit of detection. While BT-11 showed limited systemic exposure, mean fecal concentrations of BT-11 increased linearly with increasing daily oral doses (7.7, 50, and 100 mg/kg once a day) to (2.39, 21.8, and 31.9 mg/g; n = 8) on day 7 of dosing. For the most detailed clinical information, refer to the latest version of the BT-11 IB.

1.4 RATIONALE FOR STUDY

Current therapies for UC are modestly successful and have significant adverse side effects suggesting a clear medical need in this therapeutic indication. LANCL2 is broadly expressed in immune, epithelial, and muscle cells and is a potential therapeutic target for chronic inflammatory,

metabolic, and immune-mediated diseases, such as UC. BT-11 is a first-in-class modulator of LANCL2 signaling. Through its action on LANCL2, BT-11 suppresses the pathology of IBD at 2 levels: by decreasing the production of inflammatory mediators and increasing anti-inflammatory molecules in the GI tract. The therapeutic efficacy of BT-11 has been clearly demonstrated in 5 mouse models and a pig model of IBD.

Furthermore, nonclinical studies performed to date have demonstrated that the pharmacology, metabolic, and PK profile exhibited by BT-11 in experimental animal species, is predicted to be safe in humans. BT-11 displays very low systemic absorption levels and is primarily retained in the GI which is the primary disease site for UC. Given this profile, BT-11 presents a potentially improved therapeutic modality for UC. Landos intends to develop BT-11 for the treatment of UC and CD. BT-11 is safe and well tolerated at all doses evaluated and supports initiation of a phase 2 program in UC patients.

This phase 2 study will assess the proof-of-concept therapeutic efficacy of BT-11 in patients with mild to moderate UC. In this population, BT-11 may serve as a steroid- and biologics-sparing alternative that poses minimal safety risks without immunosuppression. With these benefits in mind, the study will assess the ability of BT-11 to induce clinical remission in these subjects.

1.4.1 Justification for Route of Administration

Three routes of administration of BT-11 have been evaluated preclinically in mouse models of IBD: oral, rectal, and intravenous. Histopathological examination of colons after administration of BT-11 indicated that oral and rectal administration were equally effective. Both oral and rectal BT-11 increased expression of IL-10 within the colon. In contrast, intravenous administration resulted in lower efficacy due to fast clearance through the kidneys and insufficient GI exposure to BT-11. BT-11 was stable in both gastric and intestinal fluid and resistant to metabolism within the GI tract. With no limiting stability issues, the oral route of administration was chosen.

1.4.2 Justification for Dose Selection

Preclinical studies in mouse models of IBD have displayed consistent efficacy at 8 mg/kg (500 mg human equivalent) across 5 models with diverse means of disease induction. Additional preclinical studies were conducted within a pig model of IBD to reveal therapeutic doses of 50 and 100 mg (500 and 1,000 mg human equivalent, respectively). Importantly, pigs are estimated to have a 1:1 human equivalent dosing ratio on a drug per weight basis. Further, in ex vivo studies on mouse and human primary cells, BT-11 was identified to have equal potency in each species with potent immune effects at concentrations of 100 nM. Characterization of the PK and responses to BT-11 in pig and mouse models identified that therapeutic doses resulted in colonic concentrations of BT-11 in the range of 60 to 100 µg/g. The partitioning of BT-11 from feces to tissues was in the range of 8 to 12%. Based on fecal PK from the phase 1 study of BT-11, oral dosing with 500 mg results in fecal concentrations of approximately 1 mg/g, which would be sufficient to induce the therapeutic effects of LANCL2 activation in the colon. The safety and tolerability of BT-11 has been tested up to doses of 100 mg/kg, or approximately 7.5 g of absolute dose, in humans with no differences in AEs or clinical pathology relative to placebo. At this current stage, no known dose-limiting side effects are known for BT-11 in humans. Thus, the 500 and 1,000 mg doses (in the range between the first and second cohorts of phase 1 SAD studies) are selected and are within the known and wide safety window for BT-11. For subjects continuing into the open-label extension (OLE) period, the 1,000 mg dose will be used due to the mixed responder/nonresponder population, the blinded status of the ongoing study, and the theorized absence of safety and

tolerability concerns at either dose level. OLE subjects will include prior responders to either dose of blinded study drug or placebo at Week 30, nonresponders in any dose group at Week 12, and subjects who relapsed during the maintenance phase.

1.4.3 JUSTIFICATION FOR DURATION OF TREATMENT

With the current definition of clinical remission and mucosal healing to be utilized in this study, a 12-week induction period was deemed as sufficient to be representative of the response to BT-11. BT-11 has a NOAEL greater than 1,000 mg/kg in 180-day rat and 270-day dog GLP toxicity studies and does not accumulate systemically in humans; therefore, extended daily dosing of BT-11 is not expected to increase the risk for side effects. Other industry IBD clinical studies have been conducted with similar endpoints with induction periods ranging from 8 to 16 weeks. Recent studies at 8 weeks of length have achieved mixed results in terms of mucosal healing suggesting that a longer timeframe of 12 weeks is necessary to meet this endpoint.

1.5 RISK-BENEFIT STATEMENT

Detailed information about the expected benefits and risks of BT-11 are found in the IB. The IB is the reference for the most current risk-benefit information.

Potential risks include:

- Clinical reproductive toxicity risk of BT-11 is unknown. No clinical pregnancies have been observed. To minimize risk, women planning to become pregnant are not eligible for the study and pregnancy tests will be performed throughout the study.
- Endoscopy with biopsy is generally well tolerated as in standard clinical care, however risks include discomfort, bleeding, or in rare cases perforation.

Potential benefits of study participation include contributing to the development process in an area of unmet therapeutic need. BT-11 is a first-in-class modulator of LANCL2 with oral once-daily dosing and no known dose-limiting side effects. It may offer an alternate for future patients with UC. BT-11 may decrease the production of inflammatory mediators and increase anti-inflammatory molecules in the GI tract. Participants in both BT-11 and placebo arms may experience benefit from more frequent assessments by clinical experts for management of UC.

Overall risk-benefit should be discussed with the investigator. In general, considering measures to minimize risk, the potential risks of study participation are deemed justified by the potential benefits.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 INDUCTION AND MAINTENANCE PERIOD

2.1.1 PRIMARY OBJECTIVE, ENDPOINT, AND SUMMARY MEASURES

	Objective	Endpoint	Summary Measures
Primary	To assess the efficacy and safety of oral BT-11 in inducing clinical remission at Week 12 in subjects with mild to moderate UC	Clinical remission rate at Week 12, defined using the 3-component modified Mayo Score as a rectal bleeding subscore of 0, a stool frequency subscore of 0 or 1, and an endoscopic subscore of 0 or 1	Difference in proportions between 1,000 mg dose group vs placebo group Followed sequentially by difference in proportions between 500 mg dose group vs placebo group

Abbreviations: UC, ulcerative colitis.

2.1.2 SECONDARY OBJECTIVES, ENDPOINTS, AND SUMMARY MEASURES

	Objectives	Endpoints	Summary Measures
Secondary	To evaluate the effects of BT-11 on disease activity as measured by symptoms, endoscopy, histology, and biomarkers during the 12-week induction period	Key (ranked) secondary endpoints: • Endoscopic remission rate at Week 12, defined as an MES of 0 or 1 • Endoscopic response rate at Week 12, defined as a decrease from baseline in MES of ≥ 1 point • Clinical response rate at Week 12, defined as decrease from baseline in Mayo Score of ≥ 3 points and ≥ 30%, with an accompanying decrease in the subscore for rectal bleeding of ≥ 1 point or an absolute subscore for rectal bleeding of 0 or 1 • Mucosal healing rate at Week 12, defined by a MES of 0 or 1 and a Geboes score < 3.1 • Histologic remission rate at Week 12, defined by a Geboes score < 3.1	Difference in proportions between 1,000 mg dose group vs placebo group Followed sequentially by difference in proportions between 500 mg dose group vs placebo group
		Other secondary endpoints: • Mean change in 3-component modified Mayo score from baseline to Week 12 • Mean change in partial Mayo Score from baseline to Weeks 2, 6, and 12 • Mean change in Mayo rectal bleeding subscore from baseline to Weeks 2, 6, and 12 • Mean change in Mayo stool frequency subscore from baseline to Weeks 2, 6, and 12 • Mean change in MES from baseline to Week 12 • Mean change in RHI scores from baseline to Week 12 • Mean change in fecal calprotectin from baseline to Weeks 2, 6, and 12	Difference in means between 1,000 mg and 500 mg dose groups (separately) vs placebo group
		• Clinical remission rate at Week 12, based on alternate definition (“MCS clinical remission”) of total Mayo Score ≤ 2 with all subscores ≤ 1 • Normalization of fecal calprotectin at Weeks 2, 6, and 12 in subjects with abnormal	Difference in proportions between 1,000 mg and 500 mg dose groups (separately) vs placebo group

	Objectives	Endpoints	Summary Measures
		fecal calprotectin at baseline (abnormal defined as fecal calprotectin > 250 mg/kg) • Normalization of hs-CRP at Weeks 2, 6, and 12 in subjects with abnormal hs-CRP at baseline (abnormal defined as hs-CRP > 3.0 mg/L)	
		• Mean change in hs-CRP from baseline to Weeks 2, 6, and 12 • Mean change in UC-100 score from baseline to Week 12 • Change in Robarts SIQ-UC items from baseline to Week 12	Difference in means between 1,000 mg and 500 mg dose groups (separately) vs placebo group
	To assess health-related quality of life during the 12-week induction period	• Mean change in IBDQ score from baseline to Week 12	Difference in means between 1,000 mg and 500 mg dose groups (separately) vs placebo group
	To assess the PK parameters of BT-11 during the 12-week induction period	• In the active BT-11 treatment group, BT-11 concentration in serum, feces, and tissue	Difference in means between 1,000 mg and 500 mg dose groups (separately) vs placebo group
	To evaluate safety during the 12-week induction period	• Frequency and severity of AEs	Difference in proportions between 1,000 mg and 500 mg dose groups (separately) vs placebo group
		• Changes in clinical chemistry and hematology from baseline • Results of vital signs and physical examination • ECG findings	Difference in means between 1,000 mg and 500 mg dose groups (separately) vs placebo group

Abbreviations: AE, adverse event; ECG, electrocardiogram; hs-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, Mayo Clinic Score; MES, Mayo endoscopic subscore; PK, pharmacokinetic; RHI, Robarts Histopathology Index; SIQ-UC, Symptom and Impacts Questionnaire for Ulcerative Colitis.

2.1.3 EXPLORATORY OBJECTIVES, ENDPOINTS, AND SUMMARY MEASURES

	Objectives	Endpoints	Summary Measures
Exploratory	To evaluate the effects of BT 11 on disease activity as measured by symptoms, endoscopy, histology, and biomarkers during up to 30 weeks of maintenance therapy	• Durable clinical remission, defined as clinical remission at both Week 12 and Week 30 • Durable clinical remission (defined as MCS clinical remission at both Week 12 and Week 30) • Durable clinical response, defined as clinical response at both Week 12 and Week 30 • Endoscopic remission rate at Week 30, defined by a MES of 0 or 1 • Endoscopic response rate at Week 30, defined as a decrease from baseline in MES of ≥ 1 point • Corticosteroid-free clinical remission at Week 30 • Corticosteroid-free endoscopic remission at Week 30 • Mucosal healing rate at Week 30, defined by a MES of 0 or 1 and a Geboes score < 3.1 • Histologic remission rate at Week 30, defined by a Geboes score < 3.1 • Clinical response rate at Week 30, defined as a decrease from baseline in Mayo Score of ≥ 3 points and ≥ 30%, with an accompanying decrease in the subscore for rectal bleeding of ≥ 1 point or an absolute subscore for rectal bleeding of 0 or 1	Difference in means between 1,000 mg and 500 mg dose groups (separately) vs placebo group
		• Mean change in 3-component modified Mayo score from baseline to Week 30. • Mean change in partial Mayo Score from baseline to Weeks 18, 24, and 30 • Mean change in Mayo rectal bleeding subscore from baseline to Weeks 18, 24, and 30 • Mean change in Mayo stool frequency subscore from baseline to Weeks 18, 24, and 30 • Mean change in MES from	Difference in means between 1,000 mg and 500 mg dose groups (separately) vs placebo group

		baseline to Week 30 • Mean change in RHI scores from baseline to Week 30 • Mean change in fecal calprotectin from baseline to Weeks 18, 24, and 30	
		• Normalization of fecal calprotectin at Weeks 18, 24, and 30 in subjects with abnormal fecal calprotectin at baseline (abnormal defined as fecal calprotectin > 250 mg/kg) • Normalization of hs-CRP at Weeks 18, 24, and 30 in subjects with abnormal hs-CRP at baseline (abnormal defined as hs-CRP > 3.0 mg/L)	Difference in proportions between 1,000 mg and 500 mg dose groups (separately) vs placebo group
		• Mean change in hs-CRP from baseline to Weeks 18, 24, and 30 • Mean change in UC-100 score from baseline to Week 30 • Change in Robarts SIQ-UC items from baseline to Week 30	Difference in means between 1,000 mg and 500 mg dose groups (separately) vs placebo group
	To assess health-related quality of life during up to 30 weeks of maintenance therapy	• Mean change in IBDQ score from baseline to Week 30	Difference in means between 1,000 mg and 500 mg dose groups (separately) vs placebo group
	To assess the PK parameters of BT-11 during up to 30 weeks of maintenance therapy	• In the active BT-11 treatment group, BT-11 concentration in serum, feces, and tissue	Difference in means between 1,000 mg and 500 mg dose groups (separately) vs placebo group
	To evaluate safety during up to 30 weeks of maintenance therapy	• Frequency and severity of AEs	Difference in means between 1,000 mg and 500 mg dose groups (separately) vs placebo group
		• Changes in clinical chemistry and hematology from baseline • Results of vital signs and physical examination • ECG findings	Difference in means between 1,000 mg and 500 mg dose groups (separately) vs placebo group
	To evaluate target engagement and mechanism of action	• Immunohistochemistry on formalin-fixed, paraffin-embedded colonic mucosal tissue biopsies - MPO (marker for neutrophil infiltration in tissue) - CD25 (Treg cell marker) - FOXP3 (Treg cell marker)	Summary of mean for observed and change from baseline values

		- LANCL2 (target) • Multiplex cytokine analysis in serum and tissue - TNFα, IFNγ, IL-4, MCP1, MIP1α, IL-8, IL-6 (pro-inflammatory cytokines) - IL-10 (anti-inflammatory cytokine) • Transcriptomic analysis on colonic mucosal tissue biopsies using quantitative polymerase chain reaction (qPCR) - TNFα, IFNγ, IL-4, MCP1, IL-8, IL-6 (pro-inflammatory cytokines) - IL-10, FOXP3 (anti-inflammatory cytokines) - LANCL2 (target) • Flow cytometry on colonic mucosal tissue biopsies - Th1 cells - Neutrophils - IL-10-producing cellular subsets including CX3CR1+ macrophages - Treg cells	
	To explore association of drug exposure in colonic mucosal tissue biopsies with clinical, endoscopic, histopathologic, cellular, and molecular outcomes	• Exposure-response analysis	Correlation analysis

Abbreviations: AE, adverse event; CX3CR1, CX3C chemokine receptor 1; ECG, electrocardiogram; FOXP3, forkhead box P3 (protein); hs-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; IL, interleukin; IFNγ, interferon gamma; LANCL2, lanthionine synthetase C-like 2; MCP1, monocyte chemoattractant protein-1; MCS, Mayo Clinic Score; MES, Mayo endoscopic subscore; MIP1α, macrophage inflammatory protein-1 α; MPO, myeloperoxidase; PK, pharmacokinetic; RHI, Robarts Histopathology Index; SIQ-UC, Symptom and Impacts Questionnaire for Ulcerative Colitis; TNFα, tumor necrosis factor alpha; Treg, T regulatory cells.

Additional details of exploratory analyses will be defined in the statistical analysis plan (SAP).

2.2 OPEN-LABEL EXTENSION PERIOD

2.2.1 OBJECTIVES, ENDPOINTS, AND SUMMARY MEASURES

	Objectives	Endpoints	Summary Measures
Safety	To assess the safety of the extended use of oral BT-11 in subjects with mild to moderate ulcerative colitis	• Percentage of subjects with TEAEs, SAEs, and TEAEs that lead to discontinuation of study drug at each study visit	Summary of proportions
		• Results of vital signs and physical examination	Summary of mean for observed and change from baseline values
Exploratory Efficacy	To evaluate the effects of BT-11 on measures of efficacy (based on subgroups defined in the statistical analysis plan)	• Partial Mayo Score clinical remission, defined as partial Mayo Score < 2, at each study visit • Partial Mayo Score clinical response, defined as partial Mayo Score decrease of ≥ 2 points from Day 1, at each study visit • Mean change in partial Mayo Score from Day 1 to each study visit • Mean change in Mayo rectal bleeding subscore from Day 1 to each study visit • Mean change in Mayo stool frequency subscore from Day 1 to each study visit	Summary of mean for observed and change from baseline values

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Additional details of exploratory analyses will be defined in the SAP.

3 STUDY DESIGN

This is a phase 2 randomized, placebo-controlled, double-blind, parallel-group, multicenter study with an optional OLE period. The purpose of this study is to evaluate the efficacy and safety of oral BT-11 compared to placebo in subjects with mild to moderate active UC.

This study includes 3 periods: induction, maintenance, and an optional OLE period.

Induction Period:

Following a 28-day screening period, a total of 195 subjects with mild to moderate UC (total Mayo Score 4-10; Mayo endoscopic subscore [MES] ≥ 2) are planned to be enrolled into this study from approximately 46 centers in Europe and the United States. Eligible subjects will be randomized in a 1:1:1 ratio to receive BT-11 low-dose (500 mg), BT-11 high-dose (1,000 mg) or placebo orally, once daily. Each of the treatment arms will comprise 65 subjects. The randomization will be

stratified by prior exposure to biologic therapy for UC (yes/no; exposed population limited to 30% of total sample) and corticosteroid use at baseline (yes/no).

A data lock and final induction phase data analysis of the Week 12 primary endpoint, Week 12 key ranked secondary endpoints, and Week 12 AE listings will be conducted after all subjects have reached Week 12. At the Week 12 visit, subjects who appear to be responders (and/or clinical remitters) and meet all other maintenance continuation requirements may continue blinded study drug until central endoscopy results are available (within approximately 1 week of the endoscopy) for confirmation of eligibility for the maintenance period. Subjects who are nonresponders at Week 12, or who lose response during the maintenance period or who complete the Week 30 visit will be eligible for the optional OLE period.

Maintenance Period:

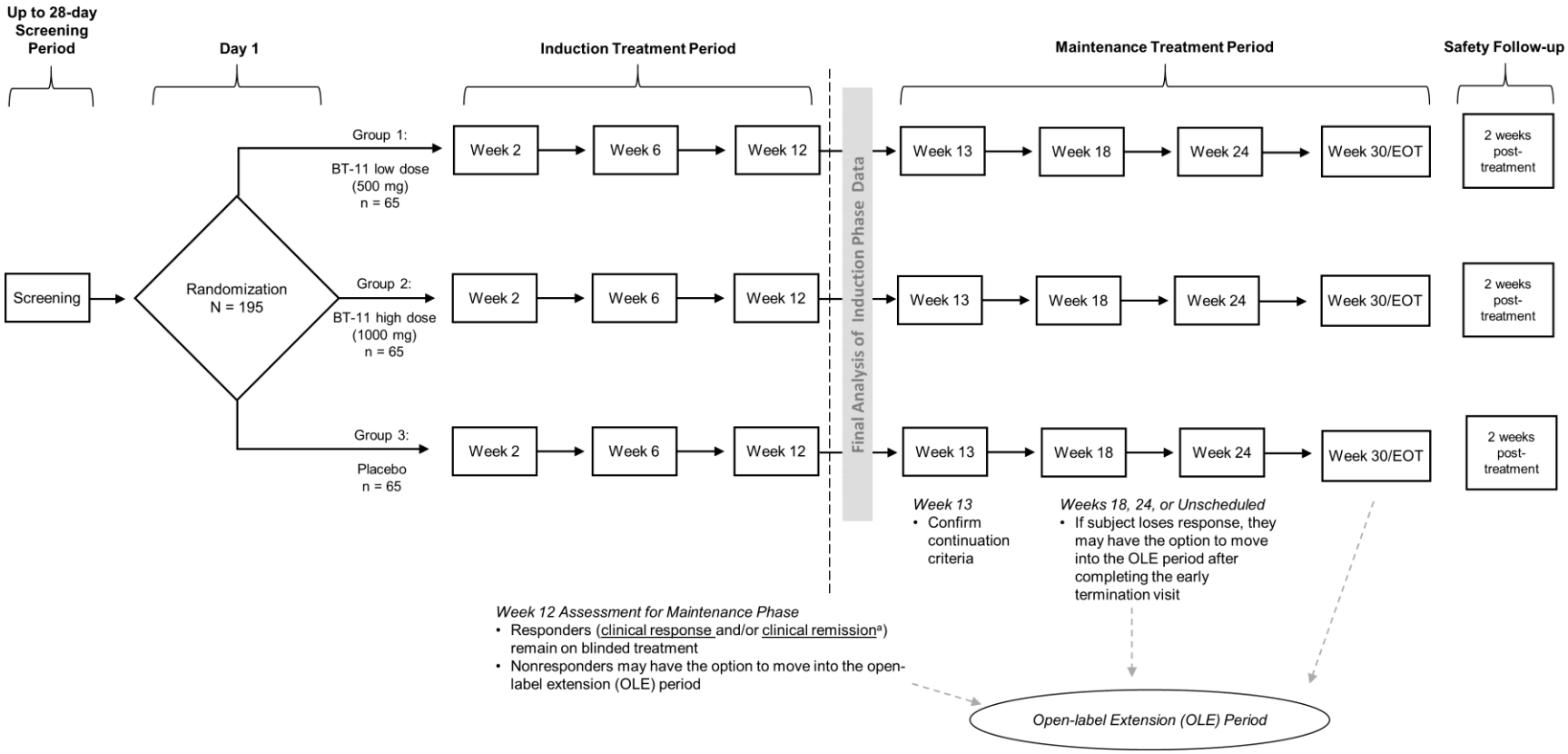
Subjects who complete the induction period and are responders at Week 12 will enter the 18-week maintenance period. Subjects who continue to the maintenance period will receive the same blinded study drug as the induction period until Week 30. If a subject loses response during the maintenance period, they may have the option to move into the OLE after completing the early termination visit.

OLE Period:

Subjects who a) completed the induction period and were nonresponders at Week 12, or b) lost response during the maintenance period, or c) completed the blinded maintenance period (through Week 30) will have the option to enter the OLE period. Subjects who are classified as nonresponders at Week 12 of the OLE will be discontinued from the study. Subjects who continue to respond to study treatment will have the option of remaining on BT-11 until the therapy becomes commercially available or the sponsor decides to terminate the study or offers an alternate OLE study.

An overview of the induction and maintenance periods is presented in Figure 1 and the OLE period in Figure 2.

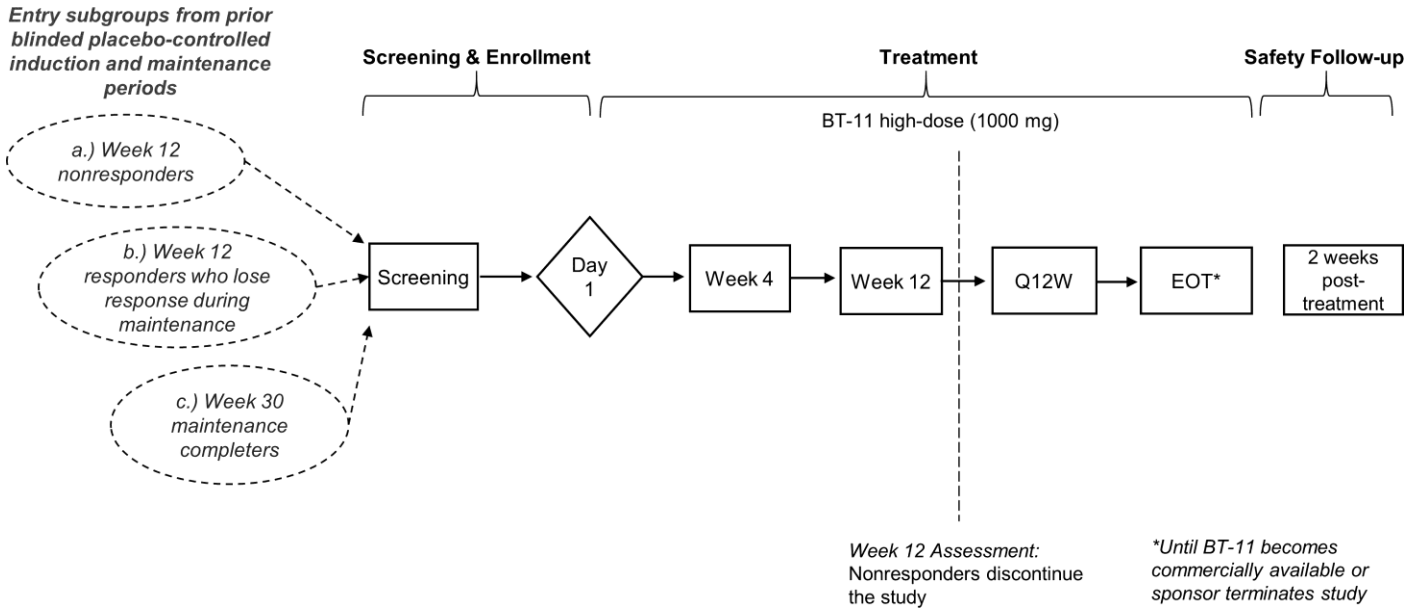
Figure 1: Overview of the Induction and Maintenance Treatment Periods



Abbreviations: EOT, end of treatment.

a Clinical response: defined as decrease from baseline in Mayo Score of ≥ 3 points and ≥ 30%, with an accompanying decrease in the subscore for rectal bleeding of ≥ 1 point or an absolute subscore for rectal bleeding of 0 or 1; Clinical remission: defined using the 3-component modified Mayo Score as a rectal bleeding subscore of 0, a stool frequency subscore of 0 or 1, and an endoscopic subscore of 0 or 1 (excluding friability from an endoscopic subscore of 1).

Figure 2: Overview of the Open-Label Extension Period



Abbreviations: EOT, end of treatment; Q12W, every 12 weeks.

4 STUDY POPULATION

The study will include 195 subjects with mild to moderate UC. Subjects with prior exposure to biologic therapy will be limited to 30% of the total sample. After 58 subjects with prior exposure to biologic therapy have been randomized into the induction period, recruitment will be limited to biologic-naïve subjects.

The specific inclusion and exclusion criteria for enrolling subjects in the study are described below.

4.1 INCLUSION CRITERIA

Subjects must meet all of the following criteria for enrollment into the study:

1. Male and female subjects aged 18 to 75 years, inclusive.
2. Diagnosis of UC for at least 3 months prior to screening.
3. Mild to moderate UC, as defined by a total Mayo Score of 4 to 10 inclusive at baseline with a MES ≥ 2 (confirmed by central reader).
4. If subjects have previously received biologic therapy for UC (i.e., TNF antagonists, vedolizumab, or ustekinumab), they must have a washout period of 8 weeks prior to randomization, and any previous failure of biologic treatment is limited to only 1 class of biologic. (Note: this inclusion criterion is only applicable until 58 subjects with prior exposure to biologic therapy have been randomized).
5. If subjects are receiving the following UC treatments, they must be on a stable dose for at least 1 month prior to randomization: 5-aminosalicylates (5-ASAs) (not exceeding 4.8 g per day), oral corticosteroids (not exceeding prednisone 20 mg, budesonide 9 mg, or equivalent).
6. If subjects are receiving bile-salt sequestrant, they must be on a stable dose for at least 3 months prior to randomization.
7. If subjects are receiving any nonprohibited medications, they must agree to maintain stable doses of concomitant medications for UC for the duration of the trial.
8. Unlikely to conceive, as defined by 1 of the following: a) subject is surgically sterilized female, b) subject is postmenopausal female ≥ 45 years of age with clinical documentation of menopause (i.e., 12 months without menses), or c) subject is male or subject is woman of child bearing potential (WOCBP), and agrees to abstain from heterosexual activity, use adequate hormonal contraception, or use double barrier contraception.
9. For WOCBP, the subject must have a negative pregnancy test at screening and within 24 hours prior to the first dose of study drug.
10. Able to participate fully in all aspects of this clinical trial.
11. Written informed consent must be obtained and documented.

4.2 EXCLUSION CRITERIA

Subjects who exhibit any of the following criteria are to be excluded from the study:

1. A diagnosis of CD, indeterminate colitis, or presence or history of fistula with CD.

2. Severe UC as per modified Truelove and Witts criteria (≥ 6 bloody stools per day and 1 or more of the following: pulse > 90 bpm, temperature > 37.8°C, hemoglobin < 10.5 g/dl, or high-sensitivity C-reactive protein (hs-CRP) > 30 mg/l).
3. Disease activity limited to distal 15 cm (proctitis).
4. Treatment with immunosuppressant (azathioprine, 6-mercaptopurine [6-MP]) within 25 days prior to randomization.
5. History of toxic megacolon, abdominal abscess, symptomatic colonic stricture, or stoma; history or is at imminent risk of colectomy.
6. History or current evidence of colonic dysplasia or adenomatous colonic polyps.
7. Current bacterial or parasitic pathogenic enteric infection, including *Clostridium difficile*, known infection with hepatitis B or C virus, known infection with human immunodeficiency virus, infection requiring hospitalization or intravenous antimicrobial therapy, or opportunistic infection within 6 months prior to screening, any infection requiring antimicrobial therapy within 2 weeks prior to screening, history of more than 1 episode of herpes zoster or any episode of disseminated zoster.
8. Live virus vaccination within 1 month prior to screening.
9. Treatment with cyclosporine, mycophenolate, tacrolimus, or tofacitinib within 4 weeks prior to randomization.
10. Treatment with intravenous corticosteroids, rectal corticosteroids, or rectal 5-ASA within 2 weeks prior to randomization.
11. Fecal microbiota transplantation within 1 month prior to screening.
12. A concurrent clinically significant, unstable, or uncontrolled cardiovascular, pulmonary, hepatic, renal, GI, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the investigator, might confound the study results or poses additional risk to the subject.
13. Known primary or secondary immunodeficiency.
14. History of myocardial infarction, unstable angina, transient ischemic attack, decompensated heart failure requiring hospitalization, congestive heart failure (New York Heart Association Class 3 or 4), uncontrolled arrhythmias, cardiac revascularization, stroke, uncontrolled hypertension, or uncontrolled diabetes within 6 months of screening.
15. Clinically meaningful laboratory abnormalities at screening, as determined and documented by the investigator.
16. Pregnant or lactating females.
17. Any surgical procedure requiring general anesthesia within 1 month prior to screening, or planned elective surgery during the study.
18. History of malignant neoplasms or carcinoma in situ within 5 years prior to screening.
19. Current or recent history of alcohol dependence or illicit drug use that in the opinion of the investigator may interfere with the subject's ability to comply with the study procedures.

20. Mental or legal incapacitation at the time of screening visit or a history of clinically significant psychiatric disorders that would impact the ability to participate in the trial according to the investigator.
21. Unable to attend study visits or comply with procedures.
22. Concurrent participation in any other interventional study.
23. Received any investigational therapy within 30 days of initiation of study drug.
24. Serious underlying disease other than UC that in the opinion of the investigator may interfere with the subject's ability to participate fully in the study.
25. Previous exposure to BT-11.
26. Prior enrollment in the current study and had received study treatment.
27. Current treatment with antimotility medications.
28. Treatment with sirolimus within 4 weeks prior to randomization.

4.3 MAINTENANCE PERIOD CONTINUATION CRITERIA

Subjects must meet all of the additional criteria for continuation in the maintenance period:

1. Responder after completing the induction period, defined by clinical response and/or clinical remission at Week 12.
2. Centrally read confirmation of response within approximately 2 weeks of completing the Week 12 Visit and able to participate fully in all other aspects of the maintenance period.
3. If subject is receiving any nonprohibited medications, they must agree to a tapering regimen for corticosteroids and to maintain stable doses of other concomitant medications for UC for the duration of the maintenance period.
4. The investigator perceives there is a favorable risk:benefit ratio for the subject to continue into the maintenance period.
5. Are unlikely to conceive, as defined by 1 of the following: a) subject is surgically sterilized female, b) subject is postmenopausal female ≥ 45 years of age with clinical documentation of menopause (i.e., 12 months without menses), or c) subject is male or subject is woman of child bearing potential (WOCBP), and agrees to abstain from heterosexual activity, use adequate hormonal contraception, or use double barrier contraception.

4.4 OPEN-LABEL EXTENSION PERIOD CONTINUATION CRITERIA

Subjects must meet all the additional criteria for continuation in the OLE period:

1. Meet one of the following criteria:
    a. Completed the induction period and were a nonresponder at Week 12 of that induction period, OR
    b. Entered the blinded maintenance period and lost response during the maintenance period, OR
    c. Completed the blinded maintenance period (through Week 30).

2. Are unlikely to conceive, as defined by 1 of the following: a) subject is surgically sterilized female, b) subject is postmenopausal female ≥ 45 years of age with clinical documentation of menopause (i.e., 12 months without menses), or c) subject is male or subject is WOCBP and agrees to abstain from heterosexual activity, use adequate hormonal contraception, or use double barrier contraception.
3. Able to participate fully in all aspects of this clinical trial. (Note: Eligible subjects will start open label treatment within approximately 2 weeks after their last dose of study drug in the induction or maintenance period).
4. If subject is on stable corticosteroids (<20 mg of prednisone/day or equivalent) from the induction period, subject must be willing to attempt to taper off corticosteroids by Week 6 of the OLE. Corticosteroids should not be started in subjects who are not receiving them at enrollment.
5. Subjects receiving 5-ASAs or purified medicinal probiotics should maintain a stable dose throughout the OLE period. Oral 5-ASAs or probiotics should not be started in subjects who are not receiving them prior to continuation in the OLE period.
6. The investigator perceives there is a favorable risk: benefit ratio for the subject to enter the OLE period.
7. Must not have experienced an SAE that was considered related to study drug during the induction or maintenance period of the study.

5 RANDOMIZATION AND BLINDING

5.1 RANDOMIZATION PROCEDURE

Eligible subjects will be randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups: BT-11 low-dose (500 mg), BT-11 high-dose (1,000 mg), or placebo through an interactive web-based response system (IWRS). After informed consent has been documented, all subjects will receive a subject number assigned by the IWRS. Following screening procedures and confirmation of all eligibility requirements, subjects will be randomized using the IWRS. Randomization will be stratified by prior exposure to biologic therapy (yes/no; exposed population limited to 30% of total sample) and current oral corticosteroid use (yes/no).

All subjects who continue to the OLE period of the study will receive BT-11 open-label therapy (1,000 mg). Open-label treatment dispensing will be managed through an IWRS.

5.2 BLINDING

During the induction and maintenance period, blinding will be maintained for the sponsor, contract research organization (CRO), investigators, site personnel, and subjects. Placebo and 500 mg and 1,000 mg BT-11 tablets will be identical in appearance. Subject randomization and treatment dispensing will be managed through an IWRS. The OLE treatment period will not be blinded.

PK samples collected during the induction and maintenance periods will be collected from all participants in order to maintain the blinding, however PK analysis is not required for placebo subjects. Personnel responsible for performing PK analyses at the central laboratory will be unblinded to subjects' treatment assignment to identify appropriate samples for analysis. Results of PK analyses will not be shared with any blinded personnel until the study is complete and unblinded, except in the case of medical emergency as described in Section 5.3. Fecal calprotectin

and hs-CRP results (after screening) will also be held by the central laboratory until the study is complete and unblinded.

After all subjects have completed the Week 12 (or end of treatment [EOT]) visit for the data lock and final induction phase analysis of the Week 12 primary endpoint, Week 12 key ranked secondary endpoints, and Week 12 AE listings, an independent statistician and a sponsor representative independent of the study team will be unblinded to all Week 12 results so that analyses can be done on the indicated Week 12 endpoints. Details of treatment assignment from the data lock and final induction phase analysis of the Week 12 primary endpoint, Week 12 key ranked secondary endpoints, and Week 12 AE listings will not be shared with any blinded personnel until the study is complete (see Section 12.5).

After all subjects have completed the Week 30 (or EOT) visit for the maintenance analysis (after maintenance data lock) the study will be unblinded.

5.3 UNBLINDING PROCEDURE

The investigator and site study personnel must remain blinded to the subject's treatment assignment. The blind should be broken only if the subject experiences a medical emergency and knowledge of the blinded treatment assignment is deemed necessary for further management of the subject.

If unblinding is deemed necessary for the safety of the subject, before breaking the blind, the investigator will contact the medical monitor to discuss the need for the unblinding. The investigator may break the blind independent of the medical monitor if the event is considered an emergency by the investigator and the code break is necessary for the appropriate medical management of the subject. The investigator must inform the medical monitor as soon as possible.

Emergency unblinding can be performed by the investigator or delegate by contacting the IWRS.

Individual code breaks by the investigator will result in withdrawal of the subject from the study. The date and reason for the code break must be documented in the source documents and on the appropriate electronic case report form (eCRF). The sponsor must be informed as soon as possible.

If required for regulatory reporting purposes or if required by local health authorities, the sponsor may unblind treatment assignment for serious, unexpected, suspected adverse reactions that are considered by the investigator or sponsor to be related to study drug (see Section 11.3.1).

6 STUDY TREATMENT

6.1 SUPPLY AND STORAGE

The study treatment will be supplied by the sponsor.

Low-dose, high-dose, and placebo study treatment will be supplied as identical-looking 1,400 mg tablets. Low-dose tablets will contain 500 mg of active BT-11. High-dose tablets will contain 1,000 mg of active BT-11. Composition of BT-11 and placebo tablets for this phase 2 study (including list of excipients) can be found in the IB.

Study treatment should be stored in refrigerated conditions (2°C to 8°C). Based on available stability studies to date, the drug product is stable for at least 18 months. Subjects are instructed to store treatment at home in the refrigerator. Detailed instructions for the storage conditions will accompany the supply shipment to the clinical study sites as appropriate for the

formulation to be administered. The storage conditions and retest date will be indicated on the label and updated as needed. The clinical trial supplies must be kept in a secure area at the study site and must be locked when not in use.

6.2 DOSAGE AND ADMINISTRATION

Subjects will take study drug by ingesting 1 tablet per day, recommended at the same time in the morning for consistency. Subjects in the low-dose group will receive 500 mg of BT-11, subjects in the high-dose group will receive 1,000 mg of BT-11, and subjects in the placebo group will receive identical looking placebo tablets. Subjects who continue to the OLE period will receive 1,000 mg of BT-11.

Additional reference information and instructions can be found in the pharmacy manual.

6.3 PACKAGING AND LABELLING

Labelling of the study treatment must conform to all requirements specified by governing regulations.

Study treatment will be packaged in opaque Alu-Alu blister packs and cartons. Blister packs and cartons will be labelled under current Good Manufacturing Practice (cGMP). Labelling follows 21 CFR (Code of Federal Regulations) 312.6. The final Alu-Alu blister packs and carton label will be coded for blinding as appropriate to the study design and in compliance with the protocol.

6.4 COMPLIANCE

Compliance with study drug will be monitored by site personnel. The first dose will be given in the clinic. If a subject is continually noncompliant with study drug, the investigator may deem it appropriate to withdraw the subject from the study. Subjects will be reminded about dosing requirements at study visits.

6.5 DRUG ACCOUNTABILITY

The investigator is responsible for study drug accountability at the site and must maintain adequate records of all study drug received and dispensed. The investigator agrees not to supply study drug to any person other than subjects participating in this study. All unused and partially used study drug must be retained at the site until inventoried by the sponsor or designee. All unused and partially used study drug will be returned to the sponsor. All materials containing the study drug will be disposed in accordance with governing regulations.

7 CONCOMITANT THERAPIES

All medications received by the subject following randomization must be recorded in the eCRF. During study participation, subjects will be asked not to take medications that are prohibited at randomization (see Section 4.2).

7.1 PERMITTED THERAPIES

The following medications are allowed at study entry, but doses must be stable for the duration of the study (with the exception of oral corticosteroids, as outlined below).

1. Oral 5-ASA, not exceeding 4.8 g per day, with stable dose for at least 1 month prior to randomization.

2. Oral corticosteroid up to a maximum of 20 mg prednisone, 9 mg budesonide, or equivalent, with a stable dose for at least 1 month prior to randomization until Week 12. After Week 12, oral corticosteroids must be completely tapered in subjects who continue in the maintenance period by Week 18. See Section 7.3 for corticosteroid tapering instructions.
3. Pain medication (nonsteroidal anti-inflammatory drug [NSAID], including low-dose 81 mg aspirin). Temporary use of opioids must be discussed and approved with the study medical monitor.
4. Bile-salt sequestrant (e.g., cholestyramine), if stable for 3 months prior to randomization.

7.2 PROHIBITED THERAPIES

The following prohibited medications must not be used at any time during the study period.

1. Immunosuppressive: azathioprine, 6-MP, methotrexate (within 25 days prior to randomization).
2. Any investigational or approved biologic therapy for UC (e.g., infliximab, adalimumab, vedolizumab, golimumab, certolizumab-pegol, ustekinumab, natalizumab) within 8 weeks prior to randomization.
3. Any investigational or approved nonbiologic therapies for UC (e.g., cyclosporine, mycophenolate, tacrolimus, tofacitinib, sirolimus) within 4 weeks prior to randomization.
4. Intravenous corticosteroids, rectal corticosteroids (within 2 weeks prior to randomization).
5. 5-ASA enemas or suppositories (within 2 weeks prior to randomization).
6. Anti-diarrheal (other than stable bile-salt sequestrant).
7. Antimotility medications.
8. Fecal transplant (within 1 month prior to screening).
9. Live virus vaccination.

7.3 CORTICOSTEROID TAPERING

Subjects who remained on stable oral corticosteroids (up to maximum of 20 mg/day from the time of study enrollment) must begin a tapering regimen at Week 12 if they continue in the maintenance treatment period of the study, and tapering should be complete by Week 18.

Suggested tapering schedules are as follows:

- For prednisone 15 or 20 mg/day (or equivalent), the dose should be reduced by 5 mg each week until a dose of 10 mg/day is reached, and then the dose should be reduced by 2.5 mg/week until discontinuation.
- For prednisone ≤ 10 mg/day (or equivalent), the dose should be reduced by 2.5 mg/week until discontinuation.
- For budesonide MMX®, a 9 mg tablet given daily may be decreased to every other day for 1 week and then discontinued.

For subjects who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms, corticosteroids may be held, increased, or re-initiated (only up to the original stable dose and not

higher) at the discretion of the treating physician. Such subjects may attempt a second corticosteroid taper, as above. However, if the second tapering attempt is unsuccessful, then the subject must be withdrawn from the study, but may remain eligible for continuation in the OLE period.

During the OLE period, subjects who are taking oral corticosteroids (i.e., those who used stable corticosteroid up to maximim of 20 mg/day allowed in the induction period) must begin a tapering regimen upon beginning the OLE period and should completely taper corticosteroid by Week 6 (as detailed above). For subjects who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms, corticosteroids may held, increased, or re-initiated (only up to their original stable dose and not higher) at the discretion of the treating physician. Such subjects may attempt a second corticosteroid taper, as above.

8 STUDY EVALUATIONS

8.1 STUDY PROCEDURES AT EACH SCHEDULED VISIT

All study evaluations and procedures with visit windows are provided in the Time and Events Schedules. Following a screening period of up to 4 weeks, the total expected duration of subject participation in the induction period will be approximately 14 weeks after randomization (12-week induction period and 2-week posttreatment safety follow-up period). Subjects who continue on to the maintenance period will be in the study for approximately 32 weeks after randomization (12-week induction period, and 18-week maintenance period) plus an additional 2-week posttreatment safety follow-up period if the subject is not continuing to the OLE period. Subjects who continue to the OLE period and who respond to OLE treatment will have the option of remaining on BT-11 until the therapy becomes commercially available, or the sponsor decides to terminate the study or offer an alternate OLE study.

Note: At the Week 12 visit, subjects who appear to be responders (clinical response and/or clinical remission) and meet all other maintenance continuation requirements may continue on blinded study drug until central endoscopy results are available (within approximately 1 weeks of the endoscopy) for confirmation of eligibility. If a subject subsequently fails to meet endoscopic criteria for responders, a final follow-up visit must be performed 2 weeks after date of last dose of study drug.

8.1.1 UNSCHEDULED VISITS

Subjects will be instructed to contact the study coordinator/investigator when any significant change in health status occurs. The subject will be asked to return for an unscheduled clinic visit if clinically indicated.

If it is determined that the subject should be withdrawn from the study, the subject will be required to complete all EOT study procedures. The subject will be asked to return for a posttreatment follow-up clinic visit 2 weeks after the date of last study drug dose.

8.1.2 POSTTREATMENT FOLLOW-UP

Subjects will be asked to return for a posttreatment follow-up visit, scheduled at 2 weeks after the last dose of study drug (14 days ± 7 days posttreatment). For subjects who are continuing to the OLE period, this W2PT visit is not required. At the posttreatment follow-up visit in the induction and maintenance period, the following study procedures will be performed:

- Physical exam
- Vital signs (temperature, blood pressure, pulse) and weight
- Clinical laboratory evaluations (hematology, serum chemistry, urinalysis)
- Fecal calprotectin
- Record AEs and concomitant medications

At the posttreatment follow-up visit in the OLE period, only the physical examination, vital signs (temperature, blood pressure, pulse) and weight will be determined, and the AE(s) and concomitant medications recorded.

8.1.3 End-of-Study Definition

The End-of-Study is defined as the end of the posttreatment safety follow-up visit 2 weeks after the last dose of study drug at the end of the OLE period (or after the last induction dose for subjects who do not continue in the maintenance period; or after the last maintenance dose for subjects who do not continue in the OLE period).

8.1.4 Poststudy Care

Access to the study drug will end after the subject's study follow-up. The investigator will ensure that poststudy care of the participant is considered.

8.2 STUDY PROCEDURE DETAILS

For timing of all study procedures, refer to the Time and Events Schedules.

8.2.1 Informed Consent Procedure

Informed consent must be obtained and documented prior to the subject entering the study and prior to any study-related procedures. The informed consent process can begin prior to Visit 1 (for example, if washout from medications is required). Additional requirements for informed consent are described in Section 13.2.

An additional informed consent form will be obtained and documented prior to the subject continuing in the OLE treatment period.

8.2.2 Demographics

Demographic information collected will include age, gender, and race/ethnicity as described by the subject.

8.2.3 Medical, Surgical, and Medication History

Medical and surgical history will include UC-related complications, other significant conditions or diseases relevant to UC, previous surgeries for UC, and the extent and duration of disease at baseline.

Medication history will include medications relevant to the eligibility criteria and any others that were stopped at or within 3 months prior to signing of the informed consent. All prior biologic medication history for the treatment of UC (with duration of previous biologic use, name of therapy, reason for discontinuation) will be collected.

8.2.4 Inflammatory Bowel Disease Questionnaire

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a disease-specific health-related quality of life (HRQOL) instrument for patients with IBD.[12] The IBDQ covers 4 dimensions: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items), and social function (5 items). Items are scored on a 7-point Likert scale and summed for a total global score in the range 32 to 224 (with higher scores indicating better HRQOL). The IBDQ has been designed to be self-administered and completed in 5 minutes.

8.2.5 Subject Diary

Subjects will complete a diary of stool frequency and rectal bleeding symptoms daily from the time of screening until the EOT visit. At screening, a reference remission stool frequency will be collected. Additional instructions are provided in Appendix 1.

8.2.6 Endoscopy with Biopsy Procedures

Subjects will undergo flexible sigmoidoscopy (colonoscopy may be performed instead for baseline endoscopy if not done in the prior 12 months) with biopsies from the area with the worst disease. Clinical sites will follow standard local procedures for endoscopy preparation. Note: screening endoscopy procedure should be scheduled at least 5 days prior to the planned randomization visit to allow for central reading.

During the induction period, 11 biopsies will be obtained from the area with the worst disease 15 to 25 cm from the anal verge, at baseline and at Week 12 (see the Time and Events Schedules). Eleven additional biopsies will be obtained during the maintenance period. If ulceration is present, the biopsy should be done from the edge of the ulcer. If no ulceration is present, then biopsy should be done from the most affected area. If mucosa appears normal (e.g., at follow-up), then random biopsies should be taken from the area 15 to 25 cm from the anal verge.

Biopsy procedures are as follows at each timepoint:

1. 2 biopsies will be placed in formalin for histopathology and immunohistochemistry
2. 2 biopsies will be snap frozen for multiplex cytokine analysis
3. 2 biopsies will be stored in a cryovial with RNAlater stabilization buffer
4. 4 biopsies will be stored in a cryovial with cryopreservation buffer for flow cytometry analysis
5. 1 biopsy for measurement of BT-11 in tissue

Samples will be processed at the study site, and then shipped to the central laboratory. Sample processing, handling, and shipping information will be defined in the central laboratory manual and the Alimentiv Inc. (Alimentiv), formerly Robarts Clinical Trials Inc, biopsy instruction card.

The endoscopy procedure will be recorded using Alimentiv Central Image Management Solutions (CIMS). Detailed instructions for setting up equipment, capturing, and transmitting endoscopic videos will be provided in a study CIMS manual.

Local site endoscopists will score the MES and enter the result in the study eCRF.

Endoscopy videos and histopathology images will be scored by qualified, independent, blinded central readers. See Section 8.2.7.

For discrepancies between local and central score for endoscopy that impact eligibility, the primary endpoint, or the Week 30 endpoint, an adjudication will be performed by a second independent central reader.

8.2.7 Central Reader Training, Scoring, and Blinding

Study central readers will be trained in the use of Alimentiv CIMS for assessment of endoscopy and histopathology (qualified gastroenterologists and pathologists, respectively). Standardized training materials will be provided to central readers.

Central readers will enter scores in a study database. Central reader scores will be the primary scores for analyses and for confirming eligibility, including for continuation in the maintenance period. In the case of adjudication, the second central reader (adjudicator) would select either the local reader or first central reader score to be used as the final score (forced adjudication).

8.2.8 Modified Mayo Score

The modified Mayo Score[13] consists of the same 4 components (stool frequency, rectal bleeding, endoscopy findings and physician's global assessment) and uses the same scoring system as the original Mayo Score.[14] Each component of the modified Mayo Score is scored from 0-3, and summed to give a total modified Mayo Score (maximum of 12 points), with higher scores representing more severe disease activity. The only difference between the modified Mayo Score and Mayo Score is that mild friability has been removed from the definition of mild endoscopic/sigmoidoscopic disease activity (endoscopic subscore of 1) in the modified Mayo Score.[13] See Appendix 2.

A 3-component modified Mayo Score will be calculated based on the sum of stool frequency, rectal bleeding, and endoscopic subscores (total range 0-9), as recommended by FDA Guidance (Draft Guidance "Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry" August 2016).[15] As in the 4-component scoring and Appendix 2, the 3-component score will also remove mild friability from the definition of mild disease activity (endoscopic subscore of 1) in line with this guidance.

8.2.9 Partial Mayo Score

The partial Mayo Score consists of 3 components of the modified Mayo Score (stool frequency, rectal bleeding, and physician's global assessment) but excludes the endoscopy subscore. The partial Mayo Score ranges from 0 to 9 with higher scores representing more severe disease activity (see Appendix 3).

8.2.10 Geboes Score

The Geboes scoring system is a stepwise ordinal grading system for histological assessment of disease severity in UC.[16] The scoring system progressively grades disease severity by assessing 7 histological items and grading histological change as grade 0 (structural change only), 1 (chronic cell infiltrations), 2A (lamina propria neutrophils), 2B (lamina propria eosinophils), 3 (neutrophils in the epithelium), 4 (crypt destruction), and 5 (erosion or ulceration). Each of the grades is subdivided into subgrades, based upon the severity of tissue abnormalities or the extent of cell infiltration (see Appendix 4). Subgrades are assessed from the worst area of the biopsy. Higher Geboes grades are indicative of more severe disease activity.

8.2.11 ROBARTS HISTOPATHOLOGY INDEX

To address the poor interrater reliability observed with the Geboes and modified Riley scoring scales,[17] the Robarts Histopathology Index (RHI) was developed by selecting items from the Geboes score that showed at least moderate intrarater reliability and best predicted scores on a visual analogue scale.[18] The 4 items selected for inclusion include: 1) the extent of chronic inflammatory cell infiltration, 2) neutrophils in the lamina propria, 2) neutrophils in the epithelium, and 4) erosions and ulceration (see Table 1). Each item is scored from 0 to 3 and multiplied by a weighting factor and summed to give the overall RHI score, with total scores ranging from 0 (no disease activity) to 33 (severe disease activity).

Table 1: Robarts Histopathology Index

Histological Variable	Grading	Multiplication Factor
Chronic inflammatory infiltrate	0=No Increase; 1=Mild but unequivocal increase; 2=Moderate increase; 3=Marked increase	X1
Lamina propria neutrophils	0=None; 1=Mild but unequivocal increase; 2=Moderate increase; 3=Marked increase	X2
Neutrophils in epithelium	0=None; 1= < 5% crypts involved; 2= < 50% crypts involved 3= > 50% crypts involved	X3
Erosion or ulceration	0=No erosion, ulceration, or granulation tissue 1=Recovering epithelium + adjacent inflammation 1=Probably erosion-focally stripped 2=Unequivocal erosion 3=Ulcer or granulation tissue	X5

Source: Mosli, et al. Gut. 2017.

8.2.12 UC-100

The UC-100 is a composite disease activity index derived from Mayo Score and RHI variables. The UC-100 is calculated as (1 + [16 × Mayo stool frequency subscore] + [6 × MES] + [1 × RHI score]), which ranges from 1 (no disease activity) to 100 (severe disease activity).[19]

8.2.13 SAMPLES FOR BIOMARKER ANALYSIS

Samples for biomarker analyses (stool samples for fecal calprotectin and hs-CRP, and serum samples for multiplex cytokine analysis) will be collected only during the induction and maintenance periods of the study.

8.2.13.1 Fecal Calprotectin

Stool samples for analysis of fecal calprotectin should be collected prior to any bowel preparation. Subjects will receive instructions and stool sample supplies for collection at home.

Fecal calprotectin results will remain blinded to the sponsor, site, and subject throughout the study.

8.2.13.2 High-sensitivity C-reactive Protein

Blood samples for hs-CRP should be collected after other clinical assessments including IBDQ, vital signs, etc., have been completed.

Hs-CRP results will remain blinded to the sponsor, site, and subject throughout the study, except for the screening result, which will be used for study eligibility confirmation.

8.2.13.3 Multiplex Cytokine Analysis

Serum samples will be collected for multiplex cytokine analysis.

8.2.14 COLLECTION OF PK BLOOD AND STOOL SAMPLES

During the induction and maintenance periods of the study, blood samples for PK will be collected as a single sample at the time of each visit with a note made of timing postdose (time of previous dose and time of PK blood sample will be collected). Stool samples for PK will be collected as close to the time of each visit as possible, with timing documented.

Blood samples for PK will not be collected during the OLE period of the study.

8.3 EFFICACY EVALUATIONS

8.3.1 INDUCTION AND MAINTENANCE PERIODS

8.3.1.1 Primary Efficacy Evaluation

To assess the efficacy of BT-11 in inducing clinical remission in subjects with mild to moderate UC, this study will evaluate the primary efficacy endpoint of clinical remission rate at Week 12, defined as a rectal bleeding subscore of 0, a stool frequency subscore of 0 or 1, and an endoscopic subscore of 0 or 1 (excluding friability in an endoscopic subscore of 1) using the 3-component modified Mayo Score.

8.3.1.2 Secondary Efficacy Evaluations

8.3.1.2.1 Key Secondary Efficacy Evaluations (Ranked)

To assess the effects of BT-11 on disease activity in subjects with mild to moderate UC, the following evaluations will be made, in the following ranked order, during the 12-week induction period:

- Endoscopic remission rate at Week 12, defined as an MES of 0 or 1
- Endoscopic response rate at Week 12, defined as a decrease from baseline in MES of ≥ 1
- Clinical response rate at Week 12 defined as decrease from baseline in Mayo Score of ≥ 3 and ≥ 30%, with an accompanying decrease in the subscore for rectal bleeding of ≥ 1 or an absolute subscore for rectal bleeding of 0 or 1
- Mucosal healing rate at Week 12, defined by a MES of 0 or 1 and a Geboes score of < 3.1
- Histologic remission rate at Week 12, defined by a Geboes score of < 3.1

8.3.1.2.2 Other Secondary Efficacy Evaluations

To assess the effects of BT-11 on disease activity in subjects with mild to moderate UC, the following evaluations will be made during the 12-week induction period:

- Mean change in 3-component modified Mayo score from baseline to Week 12

- Mean change in partial Mayo Score from baseline to Weeks 2, 6, and 12
- Mean change in Mayo rectal bleeding subscore from baseline to Weeks 2, 6, and 12
- Mean change in Mayo stool frequency subscore from baseline to Weeks 2, 6, and 12
- Mean change in MES from baseline to Week 12
- Mean change in RHI scores from baseline to Week 12
- Mean change in fecal calprotectin from baseline to Weeks 2, 6, and 12
- Clinical remission rate at Week 12, based on alternate definition ("Mayo Clinic Score [MCS] clinical remission") of total Mayo Score ≤ 2 with all subscores ≤ 1
- Normalization of fecal calprotectin at Weeks 2, 6, and 12 in subjects with abnormal fecal calprotectin at baseline (abnormal defined as fecal calprotectin > 250 mg/kg)
- Mean change in hs-CRP from baseline to Weeks 2, 6, and 12
- Normalization of hs-CRP at Weeks 2, 6, and 12 in subjects with abnormal hs-CRP at baseline (abnormal defined as hs-CRP > 3.0 mg/L)
- Mean change in UC-100 score from baseline to Week 12
- Change in Robarts SIQ-UC items from baseline to Week 12

To assess health-related quality of life during the 12-week induction period:

- Mean change in IBDQ score from baseline to Week 12

To assess the PK parameters of BT-11 during the 12-week induction period:

- BT-11 concentration in serum, feces, and tissue will be assessed at Week 12

8.3.1.3 Exploratory Evaluations

Additional exploratory efficacy evaluations will be conducted through the maintenance period (up to Week 30) as described below.

8.3.1.3.1 Exploratory Efficacy Evaluations

To assess the effects of BT 11 on disease activity during up to 30 weeks of maintenance therapy:

- Durable clinical remission (defined as clinical remission at both Week 12 and Week 30)
- Durable clinical remission (defined as MCS clinical remission at both Week 12 and Week 30)
- Durable clinical response (defined as clinical response at both Week 12 and Week 30)
- Endoscopic remission rate at Week 30 (MES of 0 or 1)
- Endoscopic response rate at Week 30 (defined as a decrease from baseline in MES of ≥ 1 point)
- Corticosteroid-free clinical remission at Week 30
- Corticosteroid-free endoscopic remission at Week 30

- Mucosal healing rate at Week 30 as defined by a MES of 0 or 1 and a Geboes score of < 3.1
- Histologic remission rate at Week 30 as defined by a Geboes score of < 3.1
- Clinical response rate at Week 30 (defined as decrease from baseline in Mayo Score of ≥ 3 points and ≥ 30%, with an accompanying decrease in the subscore for rectal bleeding of ≥ 1 point or an absolute subscore for rectal bleeding of 0 or 1)
- Mean change in 3-component modified Mayo score from baseline to Week 30.
- Mean change in partial Mayo Score from baseline to Weeks 18, 24, and 30
- Mean change in Mayo rectal bleeding subscore from baseline to Weeks 18, 24, and 30
- Mean change in Mayo stool frequency subscore from baseline to Weeks 18, 24, and 30
- Mean change in MES from baseline to Week 30
- Mean change in RHI scores from baseline to Week 30
- Mean change in fecal calprotectin from baseline to Weeks 18, 24, and 30
- Normalization of fecal calprotectin at Weeks 18, 24, and 30 in subjects with abnormal fecal calprotectin at baseline (abnormal defined as fecal calprotectin > 250 mg/kg)
- Mean change in hs-CRP from baseline to Weeks 18, 24, and 30
- Normalization of hs-CRP at Weeks 18, 24, and 30 in subjects with abnormal hs-CRP at baseline (abnormal defined as hs-CRP > 3.0 mg/L)
- Mean change in UC-100 score from baseline to Week 30
- Change in Robarts SIQ-UC items from baseline to Week 30

To assess health-related quality of life during up to 30 weeks of maintenance therapy:

- Mean change in IBDQ score from baseline to Week 30

To assess the PK parameters of BT-11 during up to 30 weeks of maintenance therapy:

- BT-11 concentration in serum, feces, and tissue will be assessed at Week 30

8.3.1.3.2 Other Exploratory Efficacy Evaluations

To evaluate target engagement and the mechanism of action of BT-11, the following exploratory endpoints will be evaluated:

- Immunohistochemistry on formalin-fixed, paraffin-embedded colonic mucosal tissue biopsies
    - MPO (marker for neutrophil infiltration in tissue)
    - CD25 (Treg cell marker)
    - FOXP3 (Treg cell marker)
    - LANCL2 (target)
- Multiplex cytokine analysis in serum and tissue

  - TNFα, IFNγ, IL-4, MCP1, MIP1α, IL-8, IL-6 (pro-inflammatory cytokines)
  - IL-10 (anti-inflammatory cytokine)
- Transcriptomic analysis on colonic mucosal tissue biopsies using qPCR
  - TNFα, IFNγ, IL-4, MCP1, IL-8, IL-6 (pro-inflammatory cytokines)
  - IL-10, FOXP3 (anti-inflammatory cytokines)
  - LANCL2 (target)
- Flow cytometry on colonic mucosal tissue biopsies including:
  - Th1 cells
  - Neutrophils
  - IL-10-producing cellular subsets including CX3CR1+ macrophages
  - Treg cells

To explore the association of exposure to BT-11 in colonic mucosal tissue biopsies with clinical, endoscopic, histopathologic, and molecular outcomes,

- Exposure-response analysis

8.3.2 OPEN-LABEL EXTENSION PERIOD

8.3.2.1 Safety Evaluations

To assess the safety of the extended use of oral BT-11 in subjects with mild to moderate UC, the following evaluations will be made during the OLE period:

- Percentage of subjects with TEAEs, SAEs, and TEAEs that lead to discontinuation of study drug at each study visit.
- Change in vital signs and physical examination results

8.3.2.2 Exploratory Efficacy Evaluations

To evaluate the effects of BT 11 on measures of efficacy (based on subgroups defined in the SAP), the following evaluations will be made during the OLE period:

- Partial Mayo Score clinical remission (partial Mayo Score < 2) at each study visit
- Partial Mayo Score clinical response (partial Mayo Score decrease of ≥ 2 points from Day 1) at each study visit
- Mean change in partial Mayo Score from Day 1 to each study visit
- Mean change in Mayo rectal bleeding subscore from Day 1 to each to each study visit
- Mean change in Mayo stool frequency subscore from Day 1 to each to each study visit

9 SAFETY EVALUATIONS

9.1 ADVERSE EVENTS

All TEAEs that occur following the signing of the informed consent will be reported on the eCRF. The incidence of TEAEs will be summarized for each treatment group by body system and

preferred term. Definitions, documentation, and reporting of TEAEs are described in detail in Section 11.

9.2 PHYSICAL EXAMINATION

A complete physical examination (general appearance, HEENT [head, eyes, ears, nose, and throat], lung/chest, heart, abdomen, skin, lymph nodes, musculoskeletal, neurological, extremities) will be performed according to the Time and Events Schedules.

9.3 VITAL SIGNS

Vital sign measurements will be obtained at each clinic visit and will include temperature, blood pressure readings, and pulse.

Body mass index (BMI) will be calculated from height and weight measurements collected at screening, Visit 5 (Week 12/induction EOT), and Visit 9 (maintenance EOT).

In the OLE period, BMI will be calculated from the height measurement collected at Visit 1 (or imported from the induction and maintenance period), and the weight measurement recorded at each OLE visit.

9.4 CLINICAL LABORATORY TESTS

Blood and urine samples will be collected and sent to a central laboratory for analysis. The timing of sample collection is outlined in the Time and Events Schedules. When possible, blood samples should be obtained after clinical assessments including IBDQ and vital signs. The following clinical laboratory tests will be performed:

- Hematology (hematocrit, hemoglobin, mean cell hemoglobin, mean corpuscular volume, red blood cell distribution width, red blood cell count, total and differential white blood cell count, basophils, eosinophils, lymphocytes, neutrophils, monocytes, reticulocytes, platelet count)
- Serum chemistry (blood urea nitrogen, creatinine, creatine kinase, total bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, sodium, potassium, chloride, bicarbonate, calcium, magnesium, inorganic phosphorus, uric acid, total protein, albumin, glucose, gamma glutamyl transferase [GGT], total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], triglycerides)
- Urinalysis (specific gravity, ketones, pH, protein, glucose, blood, nitrite, bilirubin, urobilinogen, leukocytes, microscopic examination)

In addition to the central laboratory safety tests, a serum pregnancy test will be carried out at the screening visit and urine pregnancy tests at other visits as applicable in female subjects of childbearing potential.

During the OLE period, blood and urine samples may be collected and assessed locally at investigator's discretion, as part of standard of care, for hematology, serum chemistry and urinalysis parameters.

9.5 ELECTROCARDIOGRAMS

Single 12-lead ECG will be obtained using an ECG machine that automatically reports heart rate, PR, QRS, QT, and Fridericia's corrected QT (QTcF) intervals.

Where ECG machines cannot or fail to provide automatic reports for QTcF, sites may manually calculate using the standard formula or may use the following web-based calculator for calculation of QTcF:

https://www.clinigate.com/clinicalc/corrected-qt-interval-qtc.php

When using this calculator, QT should be entered in msec and heart rate should be entered in beats/min. Per GCP, any calculation (manual or calculator) should be documented as source data. Source data should be signed by the PI or a responsible site representative reviewing ECGs and filed with the subject's study source documents.

9.6 LIVER SAFETY MONITORING

During the induction and maintenance period, if a subject experiences elevated ALT or AST ≥ 3×upper limit of normal (ULN) and either total bilirubin level (TBL) ≥ 2×ULN and/or international normalized ratio (INR) > 1.5, then repeat liver chemistry testing should be performed as soon as possible. Upon confirmation of the abnormality, retests (ALT, AST, alkaline phosphatase, bilirubin, INR) should be performed weekly until the abnormalities resolve, stabilize, or return to baseline. If the abnormality persists or worsens, clinical and laboratory monitoring should be continued by the investigator and in consultation with the study medical monitor. If at any time the subject meets stopping criteria as described in Section 10.1, permanent discontinuation of study treatment should be discussed with the study medical monitor.

During the OLE period, liver chemistry testing will be assessed locally at investigator's discretion, as part of standard of care.

10 EARLY WITHDRAWAL

If a subject is prematurely withdrawn from the study, the reason for early withdrawal must be documented in the source document and recorded in the eCRF. All EOT procedures will be performed at the time of withdrawal. The subject will be instructed to return all remaining study drug/supplies. If a subject is withdrawn due to an SAE, the subject will be followed to the resolution or stabilization of the event.

10.1 WITHDRAWAL CRITERIA

A subject may discontinue treatment for the following reasons and after discussion with the investigator and/or the medical monitor:

- Pregnancy (see Section 11.3)
- AE that compromises the subject's ability to continue study-specific procedures or where it is not considered to be in the subject's best interest to continue study drug
- At the discretion of the investigator
- Subject choice (withdrawal of consent by subject; investigator will attempt to ascertain reason)
- Protocol violation
- Noncompliance with study drug
- Noncompliance with diary entries

- A hepatic event or liver test abnormality, where considerations for discontinuation include:
  - ALT or AST > 8× ULN
  - ALT or AST > 5× ULN for more than 2 weeks
  - ALT or AST > 3× ULN and (TBL > 2× ULN or INR > 1.5)
  - ALT or AST > 3× ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

Subject should still be followed for safety assessment 2 weeks after the last study drug dose.

Reason for treatment discontinuation will be documented in the eCRF.

11 ADVERSE EVENT AND SERIOUS ADVERSE EVENT REPORTING

11.1 DEFINITIONS

11.1.1 ADVERSE EVENT

An AE is any untoward medical occurrence in a subject or clinical investigation subject that does not necessarily have a causal relationship with the administration of a pharmaceutical or an investigational product (IP). An AE can therefore be any unfavorable or unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not related to the IP. An AE may be a new illness, worsening of a sign or symptom of a condition, or an effect of the study medication, including the comparator.

Types of events the **meet** the AE definition include:

- Abnormal laboratory test results or safety assessments (ECG, vital signs) that worsen from baseline, are considered clinically significant by the investigator (and are not expected based on the subject's condition).
- New conditions detected or diagnosed after study drug initiation.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- Signs or symptoms of a possible drug interaction.
- Signs or symptoms of a suspected overdose of any medication. Overdose will not be reported as an AE unless it is an intentional overdose taken with possible suicidal or self-harming intent, which would be reported regardless of sequelae.

Types of events that **do not meet** the AE definition include:

- Laboratory findings or abnormal safety assessments associated with the subjects underlying UC, unless judged by the investigator to be more severe than expected for the subject's condition.
- Expected UC disease, signs or symptoms, unless more severe than expected for the subject's condition.
- Procedures (medical or surgical procedures such as endoscopy or appendectomy). A condition that leads to a procedure is recorded as an AE.

- Baseline medical conditions that do not worsen.

All AEs that occur during treatment (TEAEs; following the signing of the informed consent) will be reported on the eCRF.

11.1.2 ADVERSE DRUG REACTION

ADRs are all noxious and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

11.1.3 UNEXPECTED ADVERSE DRUG REACTION

An unexpected ADR is an ADR, the nature and severity of which is not consistent with the applicable product information, e.g., the IB.

11.1.4 SERIOUS ADVERSE EVENT

A SAE is any AE occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening, i.e., the subject was at immediate risk of death at the time of the event; it does not include any event that hypothetically might have caused death if it had occurred in a more severe form
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalizations and/or surgical procedures that are scheduled to occur during the study period, for an illness or disease that existed before subject enrollment in the trial, will not be considered AEs provided the pre-existing condition did not deteriorate (e.g., surgery performed earlier than the planned date)
- Results in persistent or significant disability/incapacity, i.e., resulted in a substantial disruption of a subject's ability to conduct normal life functions
- Is associated with a congenital anomaly/birth defect
- Is an important medical event, i.e., an event that may not result in death, be life-threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, and the development of drug dependency or drug abuse

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate.

Pregnancy in a study participant, occurring after randomization is considered an immediately reportable event (as described in Section 11.3).

11.2 CLASSIFICATION

11.2.1 SEVERITY

Adverse events will be classified as mild, moderate, or severe in severity as follows:

- Mild: Discomfort noticed but no disruption of normal daily activity.
- Moderate: Discomfort sufficient to reduce or affect normal daily activity.
- Severe: Incapacitating with inability to work or perform normal daily activity.

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

11.2.2 ATTRIBUTION

The relationship of the AE to study treatment will be assessed by the investigator to be not related, unlikely, possible, probable, or definite, as follows:

- Not related: No relationship between the AE and the administration of study treatment, judged clearly and incontrovertibly due to extraneous causes such as concomitant medication(s) or the subject's clinical state.
- Unlikely: The AE is more likely due to an alternative explanation such as concomitant medication(s), concomitant disease(s) and/or the time relationship suggests that a causal relationship is unlikely.
- Possible: The AE might be due to the administration of study treatment. An alternative explanation such as concomitant medication(s) or concomitant disease(s) is inconclusive. The time relationship is reasonable therefore the causal relationship cannot be excluded.
- Probable: The AE might be due to the administration of study treatment. An alternative explanation such as concomitant medication(s) or concomitant disease(s) is less likely. The time relationship is suggestive, i.e., it is confirmed by de-challenge.
- Definite: The AE is a possible ADR and cannot be reasonably explained by an alternative explanation such as concomitant medication(s) or concomitant disease(s). The time relationship is very suggestive, i.e., it is confirmed by de-challenge and re-challenge.

For the purposes of safety analyses, all SAEs classified with a relationship to study drug administration of possible, probable, or definite will be considered treatment-related events.

11.3 PROCEDURES FOR AE AND SAE REPORTING

All AEs experienced by the subject between the signing of the informed consent and discontinuation of study treatment will be reported. All AEs must be recorded in the eCRF. For both serious and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

All SAEs will be reported to Ergomed and recorded in the eCRF starting from the time of the signing of the informed consent up to and including the 2-week posttreatment visit.

All SAEs, regardless of the relationship to study treatment, must be reported within 1 working day of site personnel being notified of the occurrence of the event.

The investigator (or designee) is required to complete an SAE form and report it to the Ergomed Safety Department using the electronic data capture (EDC) system. If EDC transmission is not possible (e.g., access or system problems), then a completed SAE form must be reported by fax or email within 1 working day of awareness of event to:

Ergomed Safety Department
Email: safety@ergomedplc.com
Fax: +48 12 378 47 09

SAE forms will be provided to each study site. The initial SAE report should include at a minimum: subject number, a narrative description of the event, and an assessment by the investigator of the intensity of the event and relationship of the event to study drug. The initial SAE report received from the site should be as complete as possible. A complete follow-up SAE report must be submitted when the information, not available at the time of the initial report, becomes available. The sponsor (or designee) may request SAE follow-up information.

Pregnancy in a study participant, occurring after randomization, is considered an immediately reportable event and must be reported to Ergomed within 1 working day after the investigator has gained knowledge of it. The subject will discontinue study drug and must be withdrawn from the study. Details of the outcome of the pregnancy (e.g., full term delivery, stillbirth, congenital anomaly, miscarriage) will be collected and reported no longer than 1 month after the expected due date.

Any SAE that occurs at any time after completion of the study, which the investigator considers to be related to study drug, must be reported to Ergomed.

11.3.1 Expedited Reporting

If there are serious, unexpected ADRs (for Europe SUSAR: Suspected Unexpected Serious Adverse Reaction) associated with the use of the study drug, the appropriate regulatory agency(ies) and all participating investigators will be notified on an expedited basis following Guidance for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH-E2A) (for Europe: following the detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions).

It is the responsibility of the investigator to promptly notify the institutional review board (IRB)/independent ethics committee (IEC) of all unexpected serious ADRs involving risk to human subjects. An unexpected event is one that is not reported in the IB.

11.3.2 Monitoring of Adverse Events and Period of Observation

All AEs should be monitored to determine the outcome or until the investigator considers it medically justifiable to terminate follow-up.

All SAEs should be monitored until resolved or until the SAE is clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es).

12 STATISTICAL METHODS

Statistical considerations are briefly described below. More details on the analysis and presentation of study results will be provided in the SAP, including a detailed description of relevant study entry subgroups for specific exploratory endpoints. Individual SAPs will be finalized prior to the unblinding of treatment allocation codes for each of the study periods.

Data from the induction and maintenance periods of the study may be used for analyses in the OLE period, such as to permit analysis from the original baseline.

12.1 POPULATIONS FOR ANALYSIS

12.1.1 SAFETY ANALYSIS SET

All subjects who received at least 1 dose of study drug will be included in the safety analysis set.

12.1.2 MODIFIED INTENT-TO-TREAT ANALYSIS SET

All randomized subjects who received at least 1 dose of study drug will be included in the modified intent-to-treat (mITT) analysis set. In the event of study drug administration error, analyses on the mITT set will be performed according to the intended treatment group. The mITT set will be used for efficacy analyses.

12.1.3 PER-PROTOCOL ANALYSIS SET

All ITT subjects who do not have any major deviations from protocol will be included in the per-protocol (PP) analysis set. Major protocol deviations will be defined in the SAP and reviewed prior to unblinding. PP analyses will be performed on the primary efficacy variable.

12.2 INTERCURRENT EVENTS

The following potential intercurrent events will be considered:

- If a subject fails to taper off oral corticosteroids, the while-on-treatment strategy will be used to analyze data collected up to and including Week 12. All other endpoints that are collected after Week 12 will be treated as missing values using the hypothetical strategy.
- Subjects that initiate prohibited concomitant medications will not be removed from the analysis (treatment policy strategy).
- Subjects that are noncompliant with treatment will not be removed from the analysis (treatment policy strategy).
- If a subject discontinues from treatment, endpoints that are assessed by differences in proportions will be assessed as nonresponders, using the composite strategy. Endpoints that are assessed by the difference in means will be treated as missing values through the hypothetical strategy.

The motivation behind these strategies is to quantify the treatment effect of BT-11 under the situations where:

- Any potential confounders, as defined in the inclusion and exclusion criteria, are removed since these could lead to a dilution of the treatment effect. The study sample, overall, remains representative of the subject population.
- Failure to taper off oral corticosteroids by Week 18 does not necessarily reflect the subject's lack of response to treatment; therefore, response will not be imputed.
- Ignoring initiation of prohibited concomitant medications is consistent with the mITT strategy; however, these may also be masking nonresponse.
- Ignoring small levels of treatment noncompliance is in line with the mITT strategy.

- BT-11 was taken for 12 weeks as specified; however, situations where the patient cannot complete the course of treatment cannot be ignored.

The complete intercurrent events strategy will be described in the SAP.

12.3 EFFICACY ANALYSES

Efficacy analyses will primarily be based on the mITT set. A robustness analysis of the primary and key secondary efficacy endpoints will also be performed on the PP analysis set. Statistical tests will be 2-sided and performed at the 0.05 level of significance.

12.3.1 PRIMARY EFFICACY ANALYSIS

The primary efficacy parameter, clinical remission rate at Week 12, defined using the 3-component modified Mayo Score as a rectal bleeding subscore of 0, a stool frequency subscore of 0 or 1, and an endoscopic subscore of 0 or 1, will be assessed in the mITT set.

The proportion of subjects with clinical remission at Week 12 for each group will be tested based on a Cochran-Mantel-Haenszel test, stratified with respect to previous use of biologic therapy (yes/no) and oral corticosteroid use at baseline (yes/no).

A closed hierarchical procedure will be used to control for multiple comparisons. The order of testing will begin with high dose versus placebo at Week 12. If this result is significant at the 2-sided $P < .05$ then the low-dose versus placebo at Week 12 will be tested, followed by subsequent ranked key secondary analyses. In this regard, the first ranked secondary endpoint is similarly tested first for the high dose and subsequently for the low dose if $P < .05$ for the high dose for the first ranked secondary endpoint. Testing continues in a similar manner for the subsequent ranked secondary endpoints with high dose tested prior to low dose. If at any point in this sequential procedure the $P < .05$ is not met, the testing procedure will be terminated. All subsequent analyses would be considered exploratory.

Missing values in the primary endpoint will be imputed as nonresponders. Analyses will also be performed on the PP analysis set for confirmatory purposes.

12.3.2 SECONDARY EFFICACY ANALYSES

Categorical secondary endpoints will be analyzed as described in the primary outcome measure section (Section 12.3.1).

Continuous secondary endpoints will be summarized by treatment group using descriptive statistics (mean, median, standard deviation, minimum, and maximum) of the values at each visit and the change from baseline to each postbaseline visit.

The main analysis methods for continuous secondary endpoints at 2 or more postbaseline visits will be based on the mixed model repeated measures analysis method. The model will include fixed effects for treatment, visit, previous biologic use, previous corticosteroid use, study region (Europe, USA), baseline value, and treatment-by-visit interaction.

For continuous secondary endpoints at only 1 postbaseline visit, analysis of covariance (ANCOVA) will be applied with the model including treatment, previous biologic use, previous corticosteroid use, study region (Europe, USA), and baseline value.

For biomarkers, nonparametric methods will be used for analysis of change from baseline. BT-11 concentrations in serum, feces, and tissue will be reported, and exposures estimated.

All collected efficacy data will also be presented in by-subject listings.

Key secondary efficacy assessments (ranked for hierarchical testing procedure as described in Section 12.3.1) are:

- Endoscopic remission rate at Week 12 (MES of 0 or 1)
- Endoscopic response rate at Week 12 (defined as a decrease from baseline in MES of ≥ 1 point)
- Clinical response rate at Week 12 (defined as decrease from baseline in Mayo Score of ≥ 3 points and ≥ 30%, with an accompanying decrease in the subscore for rectal bleeding of ≥ 1 point or an absolute subscore for rectal bleeding of 0 or 1)
- Mucosal healing rate at Week 12 as defined by a MES of 0 or 1 and a Geboes score < 3.1
- Histologic remission rate at Week 12 as defined by a Geboes score < 3.1

Other secondary efficacy assessments are:

- Mean change in 3-component modified Mayo score from baseline to Week 12
- Mean change in partial Mayo Score from baseline to Weeks 2, 6, and 12
- Mean change in Mayo rectal bleeding subscore from baseline to Weeks 2, 6, and 12
- Mean change in Mayo stool frequency subscore from baseline to Weeks 2, 6, and 12
- Mean change in MES from baseline to Week 12
- Mean change in RHI scores from baseline to Week 12
- Mean change in fecal calprotectin from baseline to Weeks 2, 6, and 12
- Clinical remission rate at Week 12, based on alternate definition ("MCS clinical remission") of total Mayo Score ≤ 2 with all subscores ≤ 1
- Normalization of fecal calprotectin at Weeks 2, 6, and 12 in subjects with abnormal fecal calprotectin at baseline (abnormal defined as fecal calprotectin > 250 mg/kg)
- Normalization of hs-CRP at Weeks 2, 6, and 12 in subjects with abnormal hs-CRP at baseline (abnormal defined as hs-CRP > 3.0 mg/L)
- Mean change in hs-CRP from baseline to Weeks 2, 6, and 12
- Mean change in UC-100 score from baseline to Week 12
- Mean change in Robarts SIQ-UC from baseline to Week 12
- Mean change in IBDQ score from baseline to Week 12
- BT-11 concentration in serum, feces, and tissue

A full description of the secondary efficacy analyses will be provided in the SAP.

12.3.3 Exploratory Efficacy Analyses

Exploratory endpoints will be analyzed as described in Section 12.3.2. A full description of the exploratory efficacy analyses will be provided in the SAP.

12.4 SAFETY ANALYSES

Safety analyses will be based on the safety analysis set. Assessments will be made by evaluating all reported AEs, physical examination findings, and changes in laboratory parameters, ECGs, and vital signs (including body weight).

For continuous safety endpoints, values at each visit and the change from baseline to each visit will be summarized by treatment group using descriptive statistics (mean, median, standard deviation, minimum, and maximum). Categorical safety endpoints will be summarized by treatment group at each visit as counts and proportions. All collected safety data will also be presented in by-subject listings.

All AEs will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. AEs will be summarized by the number and percentage of subjects experiencing any AEs, any severe AEs, any drug-related AEs, any SAEs, any drug-related SAEs, and any AEs leading to study drug interruption. Adverse events will also be summarized by 1) system organ class and preferred term; 2) system organ class, preferred term, and severity; and 3) system organ class, preferred term, and relationship to study drug. If a subject experienced more than 2 AEs for a given preferred term, severity is defined by the most severe event and relationship to study drug is defined by the most related event.

Safety data will be presented by treatment groups. Descriptive statistics will be presented. No formal statistical tests will be performed.

12.5 DATA LOCKS

12.5.1 FINAL INDUCTION PHASE DATA LOCK

A data lock and final induction phase analysis of the Week 12 primary endpoint, Week 12 key ranked secondary endpoints, and Week 12 AE listings will be performed when all subjects have completed the induction period (or discontinued study treatment). To minimize any bias being introduced into the analysis, all data associated with the primary and key secondary endpoints during the assessment period must have been monitored, the induction period SAP must be finalized and approved, definitions of analysis populations must be finalized (including classification of significant protocol deviations and decision regarding exclusion of any subjects from the induction study analysis) before database lock and before unblinding.

As this will be the final analysis of the primary endpoint and the key ranked secondary endpoints, no adjustment of type I error will be performed. The induction analysis will be conducted by a limited number of preidentified team members who do not have direct site contact or data entry/validation responsibilities. Unblinding details will be specified in the unblinding plan section of the SAP or in a separate unblinding plan document. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.

12.5.2 MAINTENANCE DATA LOCK

A second analysis (maintenance data lock and analysis) will be performed to assess the remaining Week 12 secondary and exploratory endpoints and the Week 30 efficacy and safety results when all subjects have completed the maintenance period (or discontinued treatment). This will be the final analysis for many of the (non-key) secondary exploratory efficacy endpoints out to Week 30. Once the full induction and maintenance data lock is complete, the study will be unblinded.

Again, to minimize any bias being introduced into the analysis, all data during the assessment period must have been monitored, the maintenance period SAP must be finalized and approved, definitions of analysis populations must be finalized (including classification of significant protocol deviations and decision regarding exclusion of any subjects from the induction study analysis) before maintenance database lock.

The final database lock and analysis of the OLE period data will be carried out when the study ends.

12.6 SAMPLE SIZE DETERMINATION

The justification for sample size is based only on comparison of remission rates in the induction period, the primary endpoint of this study.

A sample size of 65 randomized subjects to each of 3 treatment groups, assuming an attrition rate of 3% per group, will allow evaluable data on approximately 63 subjects per group at Week 12. This sample size will allow for the detection of a 17-percentage point change in remission rates (assuming 5% placebo remission rate) between groups with a type I error rate of < 0.05 and 80% power. The placebo remission rate was estimated based on the results of a recent moderate-to-severe UC study by Sandborn et al (2016).[20] The study found that the placebo induction clinical remission rate, as determined by a 4-component Mayo score ≤2 with no subscore >1, was 6%. Accounting for the differences in study population and score method (4-component versus 3-component Mayo score), a 5% placebo rate was assumed.

12.7 HANDLING OF MISSING, UNUSED, AND SPURIOUS DATA

All available efficacy and safety data collected for the study will be included in data listings and/or summary tables. No imputation of values for missing safety data will be performed. As described in Section 12.3.1, missing values in dichotomous efficacy endpoints will be imputed as nonresponders. Missing values in continuous efficacy endpoints will be handled implicitly in the mixed model regression. As a sensitivity analysis, continuous efficacy endpoints will also be analyzed with missing values imputed using the Last Observation Carried Forward approach.

12.8 SENSITIVITY ANALYSIS

As noted in Section 12.3, a sensitivity analysis will be conducted on the primary and key secondary endpoints where subjects who initiated prohibited concomitant medication after randomization will be treated as nonresponders. As noted in Section 12.7, a sensitivity analysis will be conducted to evaluate the imputation of missing values. A full description of the sensitivity analysis will be provided in the SAP.

12.9 REPORTING OF DEVIATIONS TO ORIGINAL SAP

All deviations from the original SAP will be reported in the clinical study report.

13 ETHICAL CONSIDERATIONS

The current study will be conducted in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH-GCP) and the applicable regulatory requirements.

13.1 INSTITUTIONAL REVIEW BOARD OR INDEPENDENT ETHICS COMMITTEE

All relevant documents for this study will be submitted to an appropriate IRB or IEC for review. A signed and dated letter documenting IRB/IEC approval must be obtained prior to entering subjects at the site. The IRB/IEC must be notified of all subsequent protocol amendments.

13.2 INFORMED CONSENT

Prior to any study procedures, it is the responsibility of the investigator to fully inform the subject or legally acceptable representative, of all pertinent aspects of the study. Each subject or a legally authorized representative must give written consent prior to the subject's participation in the study. The method of obtaining and documenting the informed consent and the contents of the consent must comply with ICH-GCP and all applicable regulatory requirement(s).

13.3 CONFIDENTIALITY OF SUBJECT RECORDS

All study records containing subject details will identify the subject by initials where permitted and the assigned subject identification number. Subject information collected will comply with the requirements for the protection of privacy of individually identifiable health information.

The investigator will grant monitor(s) and auditor(s) from the sponsor or its designee and regulatory health authorities access to the subject's original medical records for verification of the data gathered and to audit the data collection process. The subject's confidentiality will be maintained, and the subject's information will be made publicly available to the extent permitted by the applicable laws and regulations.

14 ADMINISTRATIVE REQUIREMENTS

14.1 PROTOCOL AMENDMENTS

The sponsor may modify the protocol at any time during the life of the protocol. Protocol amendments will require IRB/IEC approval prior to implementation except when changes to the protocol are required to eliminate immediate hazards to the study subjects. The sponsor and IRB/IEC must be notified immediately after such changes have occurred.

14.2 PREMATURE TERMINATION OF THE TRIAL

If the investigator or sponsor discovers sufficient reasonable cause for the premature termination of the study, the terminating party will provide written notification documenting the reason for study termination. The appropriate regulatory agencies and IRB/IEC must be notified.

14.3 COMPLETION OF ELECTRONIC CASE REPORT FORMS

The investigator and site study personnel will be trained on eCRF completion. The investigator is responsible for all entries in the eCRF for completeness, accuracy, and clarity. The investigator or designee should complete the eCRF as soon as possible after the information is collected. The investigator is responsible to endorse all the information recorded in the eCRF and will provide formal approval of the final submitted data.

14.4 ACCESS TO SOURCE DATA/DOCUMENTS

The investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

14.5 QUALITY ASSURANCE

14.5.1 ONSITE MONITORING

The sponsor or its designee will perform onsite monitoring visits periodically during the study. At these visits, the monitor will review study documents to ensure adherence to the study protocol and regulatory requirements, and to review eCRF entries against source documents. Findings from the visit will be discussed with the investigator.

14.5.2 ONSITE AUDITS

The sponsor or its designee may visit the site to conduct an audit of the study in accordance with regulatory guidelines. The audit will require access to all study records and source documents for inspection. Such audits may also be conducted by IRB/IEC or regulatory authorities.

14.5.3 DATA QUALITY ASSURANCE

Study data will be entered in the eCRF by trained study personnel. Data validation edit checks will be defined and implemented. Inconsistent and questionable data detected during data entry or data validation process will be queried. Data clarification forms will be generated, and any discrepancies will be resolved.

14.6 RETENTION OF STUDY DOCUMENTS

The investigator must retain all study records for 25 years after the notification of the IRB/IEC regarding the end of the study or according to applicable regulatory requirements, or the length of time required by national or local health authorities, whichever is longer. After that period of time, study records may be destroyed as per local regulations.

If the investigator retires, relocates, or withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The sponsor must be notified in writing if a custodial change occurs.

14.7 CLINICAL TRIAL REGISTRATION AND DISCLOSURE OF RESULTS

The sponsor will register this trial on ClinicalTrials.gov before the start of the study, and post the results of the clinical trial, for public viewing.

14.8 PUBLICATION POLICY

The sponsor will own all intellectual property and data generated in this project.

In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter trials only in their entirety.

All decisions about publication of the study data will be made by the sponsor. Draft manuscripts, abstracts, and presentations should be developed by the sponsor and circulated to co-authors for review and approval. The sponsor will retain the ownership of the data obtained in this study. Authorship of publications resulting from this study should accurately reflect the contribution of individuals at the sponsor and CRO to the design and implementation of the trial, analysis of the data, and preparation of the manuscript.

14.9 CONFIDENTIALITY

All confidential information, verbal and written, provided to the investigator by the sponsor will be kept in strict confidence, and restricted to the study personnel involved in conducting the study, except if the information is required by the IRB/IEC or similar committees.

14.10 FINANCING AND INSURANCE

Financing and insurance will be addressed in a separate agreement with study centers.

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APPENDICES

APPENDIX 1 PATIENT-REPORTED OUTCOME DIARY (SUBJECT DIARY) STANDARDIZATION

Patient-reported Outcome Scoring

Stool frequency score for efficacy analyses will be based on the average score from the most recent consecutive 3-day period (excluding date of bowel preparation for endoscopy).

Rectal bleeding score for efficacy analyses will be based on the most severe rectal bleeding score among the 3 scores from the most recent consecutive 3-day period (as in the stool frequency).

Category of Instructions	Specific Instructions to Subjects
Definition of Stool	• Subject will be instructed that a stool is defined as a trip to the toilet when the subject has either a bowel movement, or passes blood alone, blood and mucus, or mucus only • Stool frequency will be recorded **daily** in a subject diary
Reference Remission Stool Frequency (over 24 hours)	• Subject will be asked to identify at the screening visit how many stools he or she had in a 24-hour period when in remission from UC • If the subject does not report that he or she has achieved remission, then the subject should be asked to identify the number of stools he or she had per day before initial onset of signs and symptoms of UC − Whether the reference remission stool frequency is based on reported stool frequency when the subject was in remission or reported stool frequency before initial onset of signs and symptoms of UC will be documented. − Both the remission and pre-UC stool frequency should be collected at baseline. This allows exploration of the natural history of pre-diagnosis stool frequency versus remission stool frequency
Most Severe Category of Rectal Bleeding (in a given 24-hour period)	• Subject will be instructed to indicate the most severe category that describes the amount of blood they had in their stools for a given day • Categories of rectal bleeding should be defined as follows: –No blood seen –Streaks of blood with stool less than half the time –Obvious blood **(more than just streaks)** or streaks of blood with stool most of the time –Blood alone passed • Subject will be instructed to select “No Blood Seen” in the rectal bleeding section if they do not have stool during a given day

APPENDIX 2 MODIFIED MAYO SCORE

Component	Mayo Score
Stool frequency	
Normal number of stools for this subject	0
1 to 2 stools more than normal	1
3 to 4 stools more than normal	2
5 or more stools than normal	3
Subscore, 0 to 3	
Rectal bleeding	
No blood seen	0
Streaks of blood with stool less than half the time	1
Obvious blood (more than just streaks) or streaks of blood with stool most of the time	2
Blood alone passes	3
Subscore, 0 to 3	
Findings on endoscopy	
Normal or inactive disease	0
Mild disease (erythema, decreased vascular pattern, **no friability**)	1
Moderate disease (marked erythema, absent vascular pattern, friability, erosions)	2
Severe (spontaneous bleeding, ulceration)	3
Subscore, 0 to 3	
Physician's global assessment	
Normal	0
Mild disease	1
Moderate disease	2
Severe disease	3
Subscore, 0 to 3	
Total score	**0-12**

Source: Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317(26):1625-1629.

Note: Mild disease definition for findings on endoscopy modified based on: Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Draft Guidance: Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry. August 2016. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM515143.pdf

APPENDIX 3 PARTIAL MAYO SCORE

Component	Partial Mayo Score
Stool frequency	
Normal number of stools for this subject	0
1 to 2 stools more than normal	1
3 to 4 stools more than normal	2
5 or more stools than normal	3
Subscore, 0 to 3	
Rectal bleeding	
No blood seen	0
Streaks of blood with stool less than half the time	1
Obvious blood (more than just streaks) or streaks of blood with stool most of the time	2
Blood alone passes	3
Subscore, 0 to 3	
Physician's global assessment	
Normal	0
Mild disease	1
Moderate disease	2
Severe disease	3
Subscore, 0 to 3	
Total score	**0-9**

Source: Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317(26):1625-29.

APPENDIX 4 GEBOES SCORE

Grade 0	**Structural (architectural change)**
Subgrades	
0.0	No abnormality
0.1	Mild abnormality
0.2	Mild or moderate diffuse or multifocal abnormalities
0.3	Severe diffuse or multifocal abnormalities
Grade 1	**Chronic inflammatory infiltrate**
Subgrades	
1.0	No increase
1.1	Mild but unequivocal increase
1.2	Moderate increase
1.3	Marked increase
Grade 2	**Lamina propria neutrophils and eosinophils**
2 A Eosinophils	
2 A.0	No increase
2 A.1	Mild but unequivocal increase
2 A.2	Moderate increase
2 A.3	Marked increase
2B Neutrophils	
2B.0	None
2B.1	Mild but unequivocal increase
2B.2	Moderate increase
2B.3	Marked increase
Grade 3	**Neutrophils in epithelium**
3.0	None
3.1	< 5% crypts involved
3.2	< 50% crypts involved
3.3	> 50% crypts involved
Grade 4	**Crypt destruction**
4.0	None
4.1	Probable – local excess of neutrophils in part of crypt
4.2	Probable – marked attenuation
4.3	Unequivocal crypt destruction
Grade 5	**Erosion or ulceration**
5.0	No erosion, ulceration, or granulation of tissue
5.1	Recovering epithelium + adjacent inflammation
5.2	Probable erosion – focally stripped
5.3	Unequivocal erosion
5.4	Ulcer or granulation tissue

Source: Geboes K, et al. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut. 2000 Sep;47(3):404-9.